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ONCOLOGY OVERVIEW

Selected Abstracts on

Liposomes

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Selected Abstracts
on

Liposomes

Eric G. Mayhew, Ph.D.
Consulting Reviewer

A SERVICE OF THE INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM
OF THE NATIONAL CANCER INSTITUTE

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INTRODUCTION

This ONCOLOGY OVERVIEW on liposomes is a compilation of abstracts published mainly from 1976 to 1981, selected from the CANCERLIT computerized data base. Some earlier abstracts and citations have been included for historical perspective. The strategy used for the on-line literature search is available upon request from the CIDAC-VIB office, and can be entered at any MEDLARS/MEDLINE terminal system in order to obtain continuing updates on this topic.

The scope of this ONCOLOGY OVERVIEW includes literature on liposomes as carriers of antitumor agents and other substances, as well as research utilizing liposomes to investigate cell and viral membrane properties. Basic studies on the preparation and physicochemical properties of liposomes are presented. Interactions of liposomes with various chemicals, drug entrapment, and oxidation and radiation damage to liposomes are covered. Also overviewed are proposed mechanisms for the cellular uptake of liposomes and their contents, and in vitro effects of liposomal components on cell growth. In vivo studies on pharmacokinetics and efficacy of liposomes as drug carriers in animals and humans, the use of hyperthermia and immunologic targeting to improve drug localization, and immunologic investigations utilizing liposomes are also reviewed.

This ONCOLOGY OVERVIEW was prepared by Eric G. Mayhew, Ph.D. (Editor), of the Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York, and Deborah Liss-Suter, B.A., of the CIDAC for Virology, Immunology and Biology, The Franklin Research Center, Philadelphia, Pennsylvania.

EDITORIAL COMMENTARY

The basic properties and characteristics of phospholipid vesicles (liposomes) as membrane models were described by Bangham et al. in 1965 (1). Since that time liposomes have been found to be useful membrane models with respect to investigations of the functions of lipids in membranes, lipid-protein interactions, mechanisms of action of membrane-active agents and reconstitution of functional membrane proteins and receptors. Furthermore, it was observed that many substances, including drugs, could be trapped in liposomes. Since Gregoriadis and Ryman (1972) suggested that liposomes could be used as drug carriers in vitro and in vivo (2), investigations of liposomes as a drug carrier system have been reported for a number of diverse systems, and studies with cancer chemotherapeutic agents have been extensive. Much of this work has revealed a probably unanticipated degree of complexity of multidisciplinary problems which must be overcome in order to develop liposomes as a useful drug carrier system. Because of the wide potential flexibility of liposomes as a drug delivery system, it is important that these now defined problems are solved in a systematic manner.

One attractive feature of liposomes is that an infinitely wide variety of types can be made, varying with respect to liposomal lipid composition, insertion of non-lipid substances into and onto the bilayer, number of lamellae (phospholipid-aqueous space layers) and size distribution. Liposome components must be of a defined purity, due to marked alterations in liposome properties that can be caused by minor impurities and by degradation. A standardized nomenclature for liposome preparations has been proposed (3) as a means of enabling investigators to directly compare liposomes made in different laboratories. Other important data useful for standardization include liposome stability during storage as well as in biological environments (in vitro and in vivo), and the efficiency of drug entrapment in terms of moles of drug per mole of liposomal lipid and non-lipid components.

Only relatively recently has it been recognized that liposome size and stability in vivo may be key determinants of their mode of action in tumor systems. Further refinements in the methodology of liposome preparation, studies of their interactions in the biological environment, particularly in the bloodstream, and designing appropriate liposomes for various drugs are still required. These parameters should be evaluated prior to the experimental use of liposome-entrapped drugs in tumor systems.

Assuming that injected liposomes remain intact long enough to reach their site of action, an understanding of factors involved in their interaction with cells and tissues may provide insight into ways to facilitate their cellular uptake. It is probable

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that liposomes initially adsorb to cell surfaces, followed by endocytotic uptake of the intact or damaged liposomes and/or fusion of liposomal and cellular membranes. Although endocytosis of some liposome types by naturally occurring phagocytic cells has been demonstrated in vivo, cellular uptake by fusion has not. However, as the fusion mechanism offers a method of overcoming natural permeability barriers to drugs, including drug resistance due to transport defects, if means are found to induce fusion in vivo (and more definitively in vitro) an important step in their development will have been reached. It is also important to determine the ability of intact liposomes to penetrate nonfenestrated capillary endothelia, and to study possible methods for penetrating these barriers in order for liposomes carrying drugs to reach target cells. Otherwise, the best that can be hoped for is locaization in the general area of the target cells, which may still be a marked improvement compared to the distribution of "free" drug.

After injection of liposomes into animals their most important organ of uptake is the liver, followed by the spleen, probably by reticuloendothelial cells in those organs. There is the possibility that the strong endocytotic uptake of liposomes by reticuloendothelial cells such as macrophages may be exploitable in cancer chemotherapy. However, the first practical clinical use of liposome-entrapped drugs will probably be the treatment of arasitic diseases, such as Leishmaniasis, where the parasites spend part of their life cycle in the liver macrophages (Alving et al., 1978 (4)). Conversely, the development of methods to reduce the reticuloendothelial uptake of liposomes will be important in treating diseases of other organ systems with encapsulated drugs, and studies using appropriate liposome types have shown this may be feasible.

Other than by taking advantage of the serendipitous strong uptake of liposomes by the liver and to a lesser extent the spleen, deliberate targeting of liposomes, and indeed of other drugs and/or carriers to specific sites, is difficult. By increasing liposome size, liposome distribution can be markedly altered, and lung uptake can be augmented. The use of liposomes to increase drug uptake into cells of the lymphoid system has been reported. Other targeting systems involving, for example, specific cell or tissue antigen-antibody interactions, although showing promise in vitro, have not as yet been clearly demonstrated in vivo. The release of drugs from heat-labile liposomes by local hyperthermia appears encouraging. Other local release methods may also provide increased specificity in drug delivery.

Studies of lipsome-entrapped antitumor drugs must be interpreted in terms of the many reservations and possibilities mentioned above. At this time most of the major classes of antitumor drugs have been entrapped, and some have been tested and shown to have antitumor activity. However, it can be stated that in animal systems, the efficacy of liposom-entrapped drugs has not yet been shown to have proven clear therapeutic advantage compared to the

optimal treatment schedule of the "free" drug, although marked alterations in the pharmacokinetics and pharmacodynamics of some antitumor agents have been demonstrated. Some studies clearly indicate that liposomes act in vivo as a type of slow-release system. It is probable that even if liposomes are able to be specifically targeted to cells or tissues, their slow-release feature will remain an important additional action mechanism.

Liposomes show some potential as immunological adjuvants for viral antigens; they may have potential in vaccine production as well as being useful tools for investigating complement-induced immune lysis. These immunological properties, in addition to the strong uptake of liposomes by cells of the reticuloendothelial system which may stimulate the tumoricidal properties of these cells, may be important areas for exploitation in cancer therapy.

The status of investigations into liposomes as antitumor drug carriers is still at an early developmental stage. Successful use of liposomes will require careful work concerning various aspects of their preparation and delivery. It is hoped that the abstracts presented in this OVERVIEW will emphasize the diversity of problems to be faced and stimulate insight into possible solutions. The time for careful design of liposomes appropriate for specific purposes has arrived, replacing the necessary but possibly over-enthusiastic and widely scattered approach of the recent past.

REFERENCES

1. Bangham, A. D., Standish, M. M. and Watkins, J. J. Mol. Biol. 13:138, 1965.

2. Gregoriadis, G. and Ryman, B. E. Eur. J. Biochem. 24:485, 1972.

3. Ann. N. Y. Acad. Sci. 308, 367-369, 1978.

4. Alving, C. R., Steck, E. A., Manson, W. L., Loizeaux, P. S., Chapman, W. L. and Waits, V. B. Life Sciences 22:1021, 1978.

ABSTRACTS

I. PREPARATION OF LIPOSOMES

1. CHAPTER I. PREPARATION AND USE OF LIPOSOMES AS MODELS OF BIOLOGICAL MEMBRANES.

Bangham AD, Hill MW, Miller NGA
Biophysics Unit, A.R.C., Institute of Animal Physiology, Babraham, Cambridge, England
Methods in Membrane Biology. Vol. 1, pp. 1-68, 1974.

2. LARGE VOLUME LIPOSOMES BY AN ETHER VAPORIZATION METHOD.

Deamer D, Bangham AD
Biophysics Unit, Institute of Animal Physiology, Babraham, Cambridge, England
Biochim Biophys Acta; 443:629-634 1976

3. SINGLE BILAYER LIPOSOMES PREPARED WITHOUT SONICATION.

Batzri S, Korn ED
Section on Cellular Biochemistry and Ultrastructure, Laboratory of Biochemistry, National Heart and Lung Institute, NIH, Bethesda, MD 20014
Biochim Biophys Acta; 298:1015-1019 1973

4. A SIMPLE METHOD OF FORMING LARGE VOLUME LIPOSOMES (MEETING ABSTRACT).

Behrens BC
Dept. Human Oncology, Univ. Wisconsin, Madison, WI, 53792
Fed Proc; 38(3,part1):370 1979

We have devised a simple method of reproducibly forming liposomes with a sequestered internal vol larger than that of hand-shaken liposome preparations. A soln of lipids in ether is sprayed over the surface of a warm aqueous soln of the molecule(s) to be entrapped, using an all-glass insufflator and pressurized N2. The resulting liposomes are left undisturbed for 2 hr at 20 C, then vortexed for 5 min. The results obtained with phosphatidylcholine/dicetyl phosphate/cholesterol (molar ratio 7/2/1) liposomes formed using a 0.17 Mole/l D-glucose in 0.05 Mole/l phosphate buffer, pH 7.4 are tabulated. The data suggest that sprayed lipsomes are larger, with fewer concentric lipid bilayers, than hand-shaken liposomes. Sprayed liposomes compared favorably with large vol liposomes formed by other more complex methods, and may be of use as vehicles for drug delivery. (no Refs)

5. PROCEDURE FOR PREPARATION OF LIPOSOMES WITH LARGE INTERNAL AQUEOUS SPACE AND HIGH CAPTURE BY REVERSE-PHASE EVAPORATION.

Szoka F, Papahadjopoulos D
Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263
Proc Natl Acad Sci USA; 75(9):4194-4198 1978

6. COMPARATIVE PROPERTIES AND METHODS OF PREPARATION OF LIPID VESICLES (LIPOSOMES).

Szoka F, Papahadjopoulos D
Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263
Ann Rev Biophys Bioeng; 465-506 1980

7. RECONSTITUTION OF BIOLOGICAL MEMBRANES.

Razin S
Department of Clinical Microbiology, The Hebrew University, Hadassah Medical School, Jerusalem, Israel
Biochim Biophys Acta; 265:241-296 1972

II. PHYSICOCHEMICAL PROPERTIES OF LIPOSOMES

A.
Molecular structure of liposomes and lipid bilayers

8. SPHINGOMYELINS IN BILAYERS AND BIOLOGICAL MEMBRANES.

Barenholz Y, Thompson TE
Dept. Biochemistry, Haddassah Medical Sch., Hebrew Univ., Jerusalem, Israel
Biochim Biophys Acta; 604(2):129-158 1980

Physical properties of sphingomyelins are discussed. Included are molecular structure; formation of monomolecular films at the air/water interface; thermotropic behavior; and molecular motions of the hydrophobic, interface, and headgroup regions. Interactions of sphingomyelins with phosphatidylcholine, cholesterol, and proteins are addressed. The markedly different physical characteristics of sphingomyelin and phosphatidylcholine, and variations in their relative amounts in bilayers and in biological membranes have profound effects on the system properties of the bilayer. Perhaps the most striking difference is in temperatures of the gel-liquid crystalline phase transition exhibited by both of these types of molecules in bilayer. In addition, cholesterol also strongly influences the phase behavior of bilayers comprised of these two choline-containing lipids. Thus the microscopic phase configuration of simple bilayer systems is markedly affected by the relative concentration of sphingomyelin, phosphatidylcholine and cholesterol. By inference, the same situation exists in the bilayers of plasma membranes of cells. Distribution of sphingomyelin in biological

systems is discussed and this is related to aging and pathological conditions. The role of sphingomyelin in membrane integrity is also addressed. It is clear that properties of bilayers comprised of sphingomyelin and phosphatidylcholine reflect differences in molecular structure. Although the details of the relationships between molecular structure and properties and the system properties of bilayers are not completely understood, molecular explanations for certain of the physiologically important properties of biological membranes are beginning to emerge. (192 Refs)

9. ANGLE OF TILT AND DOMAIN STRUCTURE IN DIPALMITOYL PHOSPHATIDYLCHOLINE MULTILAYERS.
Birrell GB, Griffith OH
Dept. Chemistry, Univ. Oregon, Eugene, OR 97403
Arch Biochem Biophys; 172(2):455-462 1976

A cooperative alignment of lipid chains in dipalmitoyl phosphatidylcholine (DPPC) bilayers was detected by using oriented multilayers containing small amounts of spin-labeled phosphatidylcholine. A significant angle of tilt exists along the entire length of the lipid chains in DPPC. This behavior is compared with that of the more complex egg phosphatidylcholine bilayers. The lipid chains do not have the alignment of a single crystal but evidently exist in domains consisting of either clusters within a bilayer or successive layers out of register in the stacked multilayer.

10. RANDOM CLOSE-PACKED ARRAYS OF MEMBRANE COMPONENTS.
Cornell BA, Chapman D, Peel WE
Dept. Biochemistry, Royal Free Hosp., 8 Hunter St., London, WC1N 1BP, England
Chem Phys Lipids; 23(3):223-237 1979

In order to provide insight into two dimensional bilayer structures, simulated lipid-protein and lipid-cholesterol arrays were constructed using discs of appropriate dimensions. The fraction of small discs (lipid chains) in contact with one large disc (protein) rises to a relatively sharp max at a ratio 2:1 (pairs of small discs/large discs). The fraction of small discs in contact with other small discs decreases with increasing concentrations of large discs; the av number of small discs contacting a large disc is approx 8, while the max possible is 12. In cholesterol lipid systems, the fraction of small discs in contact with one cholesterol molecule (chl) increases slowly to a broad max at a ratio of 1:2 (small disc/chl). At a small disc/chl ratio of 3:1, each chl molecule contacts an av of one other chl and four or five small discs. The number of spontaneous contacts between molecules in random, close-packed systems can be deduced from curves constructed from the data. The consequences of random packing of membranes are examined. (29 Refs)

11. MOLECULAR PACKING OF HIGH DENSITY LIPOPROTEINS: A POSTULATED FUNCTIONAL ROLE.
Segrest JP
Dept. Pathology, Comprehensive Cancer Center, Birmingham, AL 35294
FEBS Lett; 69(1):111-115 1976

A postulated functional role for the molecular packing of high density lipoproteins (HDL) is described. Cholesteryl ester has three possible orientations in HDL. As an extended molecule, it could be oriented with its steroid ring pointed outward and the fatty acyl chains at the HDL center or with the steroid ring at the HDL center; as a third possibility, it could exist in a compact folded conformation. The similarities of the freedom parameters of phospholipid head groups in *liposomes* and HDL indicate small likelihood of a tight electrostatic interaction between the amphipathic helixes and head groups in the intact lipoprotein, since the surrounding water would be competing for charged groups. The freedom parameters of phospholipid head groups in HDL are sensitive to the number of amphipathic helixes buried in the outer surface vol. It is suggested that a mechanism exists for controlling the rate of exchange of cholesterol and phospholipid between individual lipoprotein particles and between cell membranes and HDL. (29 refs)

12. THE USE OF BIMOLECULAR LIPID MEMBRANES FOR SELECTION OF BIOLOGICALLY ACTIVE COMPOUNDS. III. THE EFFECT OF STEROID COMPOUNDS ON THE STRUCTURE AND PERMEABILITY OF BIMOLECULAR LIPID MEMBRANES.
Kats MM, Nizhny SV
Scientific Res. Inst. Biological Trials Chemical Compounds, Moscow Oblast, USSR
Khim Farm Zh; 11(10):6-12 1977

Literature pertaining to the effect of steroid compounds on the permeability of bimolecular lipid membranes (BLM) is reviewed. On the basis of the type of interaction with BLM, three groups of steroids can be recognized. Group 1 includes cholesterol-like compounds, with an isooctyl chain in position 17, which decrease the permeability of BLM to nonorganic ions. Group 2 includes compounds with polar fragments on the opposite ends of the molecule (deoxycorticosterone, progesterone), which increase the permeability of bilayers. Group 3 includes the polar steroid compounds (cortisone, hydrocortisone), which decrease the permeability of BLM to nonelectrolytes. (30 Refs)

13. ROLE OF LIPID IN MEMBRANE STRUCTURE AND FUNCTION.
McConnell HM
Cellular Membranes and Tumor Cell Behavior A Collection of Papers Presented at the Twenty-Eighth Annual Symposium on Fundamental Cancer Research, 1975. The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas Baltimore, The Williams and Wilkens Company, 1975.

The physical-chemical properties of lipids and lipid-protein interactions are reviewed as part of a study to develop methods for detecting specific lateral and transmembrane interactions between membrane components. Reconstituted phospholipid membranes containing selected components isolated from biological membranes were used. Endothermic phase transitions in phosphatidylcholines, such as dimyristoylphosphatidylcholine (DMPC), have been studied extensively. An important feature of the lipid bilayer above the transition temperature is that the hydrocarbon chain motions are highly correlated in neighboring molecules. When the properties of a binary mixture of membrane components are considered, solid-phase miscibility is typical of pairs of phospholipid molecules having similar molecular structures; eg, DMPC and dipalmitoylphosphatidylcholine. For pairs of phospholipids having increasingly dissimilar molecular structures, miscibility in the solid phase becomes more limited. Studies of freezing point depression of phospholipids indicate that it may be possible to detect and study strong, specific lateral (or transmembrane) interactions between membrane components present as solutes at low concentrations in pure or mixed phospholipid bilayer membranes. The correlated motion of neighboring fatty acid chains will limit the applicability of lipid freezing-point depressions for the determination of specific lateral interac-

tions between membrane components but various alternative approaches, such as using spin labels or other physical measurements, may be used. Very little is known about the isothermal biophysical response of lipids to biochemical signals in intact cells but fatty acid spin labels bound nonspecifically to erythrocyte membranes are responsive to physiological concentrations of the prostaglandins PGE, and PGE2 , acetylcholine, epinephrine, cAMP, and cholera toxin. This suggests that the biophysical state of the lipids in the erythrocyte is affected by physiologically relevant biochemical changes in the erythrocyte and it is likely that the changes arise in some way from changes in lipid-protein interactions. (67 refs)

14. SCANNING CALORIMETRIC EVIDENCE FOR A THIRD PHASE TRANSITION IN PHOSPHATIDYLCHOLINE BILAYERS.

Chen SC, Sturtevant JM, Gaffney BJ

(c/o Sturtevant) Dept. Chemistry, Yale Univ., New Haven, CT, 06511

Proc Natl Acad Sci USA; 77(9):5060-5063 1980

A third phase transition, centered at about 18 C, was observed by differential scanning calorimetry in a multilamellar suspension of dipalmitoyl phosphatidylcholine that had been held at 0 C for several days. This transition is less cooperative than the other two transitions which are well known for this system, and it is accompanied by an enthalpy increase about 3x as large as that of the so-called pretransition at 35 C and about half that of the main gel to liquid crystal transition at 41 C. The reversal of this transition on cooling is extremely slow. (Author abstract) (6 Refs)

15. MULTIPLE THERMOTROPIC STATE TRANSITIONS IN ERYTHROCYTE MEMBRANES; A LASER-RAMAN STUDY OF THE CH-STRETCHING AND ACOUSTICAL REGIONS.

Verma SP, Wallach DF

Division of Radiobiology, Department of Therapeutic Radiology, Tufts-New England Medical Center, 171 Harrison Avenue, Boston, Mass. 02111, U.S.A.

Biochim Biophys Acta; 436(2):307-318 1976

We have examined the Raman scattering from erythrocyte ghosts at 2700 cm(-1) - 3000 cm(-1) (CH-stretching region), that at low frequencies due to acoustical vibrations, as well as that due to nu (-C=C-) and nu (=C-C=) of beta-carotene, in the temperature range of -30 degrees C to + 30 degrees C. For comparison we have also evaluated the Raman spectra of *liposomes* composed of lecithins plus or minus cholesterol. Plots vs temperature of the intensities (I) of the approx 2880 cm(-1) and 2932 cm(-1) bands relative to the intensity of the thermally stable 2850 cm(-1)band, ie the (I2880/I2850) and (I2932/I2850) ratios, reveal discontinuities in both erythrocyte membranes and liposomes. In erythrocyte membranes, plots of (I approx 2880/I2850) and (I approx 2932/I2850) reveal several discontinuities. Those reported by (I approx 2880/I2850) occur at + 17 degrees C and approx -4 degrees C. The ratio (I approx 2932/I2850) reveals a transition between -20 degrees C and +10 degrees C, 1/2 maximal at -8 degrees C. The ratio (I1527/I1158), representing the relative intensity of nu (-C=C-) vs nu (=C-C=) of membrane-bound beta-carotene, changes discontinuously with the 17 degrees C transition, but is stable over the rest of the temperature range studied. The data indicate that a major membrane-state transition takes place below 0 degrees C but that an additional transition occurs at approx 17 degrees C. (Author Abstract)

16. EFFECT OF MELITTIN ON THERMOTROPIC LIPID STATE TRANSITIONS IN PHOSPHATIDYLCHOLINE LIPOSOMES.

Verma SP, Wallach DF

Tufts-New England Medical Center, 171 Harrison Ave., Boston, Mass. 02111

Biochim Biophys Acta; 426(4):616-623 1976

The Raman scattering due to CH stretching vibrations, as well as to v(-C=C-), and to v(=C-C=) of beta-carotene, of liposomes composed of phosphatidylcholine (egg, dimyristoyl, dipalmitoyl) +/- cholesterol, beta-carotene or melittin in the temperature range of -10 C to +45 C were examined. Plots versus temperature of the intensities of the 2885 cm(-1) and 2930 cm(-1) CH stretching bands relative to the intensity of the thermally stable 2850 cm(-1) band (i.e the I2885 /I2850 and I2930 /I2850 ratios), revealed a sharp discontinuity in cholesterol-free phosphatidylcholine liposomes; this coincided with the gel to liquid-crystal transition temperature of the fatty acyl chains. In cholesterol/phosphatidylcholine liposomes the change in I2885 /I2850 occured over a very broad temperature range and I2930 /I2850 remained stable. I1527 /I1158 , (i.e the intensity of v(-C=C-) relative to that v(=C-C=) in beta-carotene/phosphatidylcholine liposomes) changed discontinuously at the gel to liquid-crystal transition temperature. The values above the transition temperature approached those of the carotenoid in organic solution. The transitions reported in I2885 /I2850 for phosphatidylcholine/melittin liposomes (25-26 : 1, M/M) were shifted to much higher temperatures than observed in phosphatidylcholine liposomes. With dimyristoyl phosphatidylcholine/melittin, the change in I2930 /I2850 also occurred at a higher temperature (28 C) than without melittin (21 C), but the temperature shift was less than the +13 C observed for I2885 /I2850 . Apparently the apolar moiety of melittin organizes phospholipids, adjacent to and more remote from the peptide moiety, to form complexes with an elevated lipid transition temperature. However, this is not necessarily a property that is shared by all proteins that interact hydrophobically with phosphatidylcholines. The effect of the peptide moiety is greater on the methylene segments (I2885 /I2850) than on the methyl termini (I2930 / I2850).

17. CAROTENOIDS AS RAMAN-ACTIVE PROBES OF ERYTHROCYTE MEMBRANE STRUCTURE.

Verma SP, Wallach DF

Tufts-New England Medical Center, 171 Harrison Ave., Boston, Mass. 02111

Biochim Biophys Acta; 401(2):168-176 1975

Resonance-enhanced Raman bands are exhibited by RBC ghosts at 1530 cm(-1) and 1165 cm(-1) attributable to v(-C=C-) and v(=C-C=), respective, of the conjugated polyene chains in carotenoids. These resonance bands lie at 1527 and 1157 cm(-1) in lipid extract of ghosts, indicating the presence of membrane-bound beta-carotene. The resonance-enhanced Raman spectrum of beta-carotene in lecithin *liposomes* is identical to that obtained with hexane or chloroform solutions. Increasing the proportion of cholesterol in cholesterol-lecithin liposomes up to a cholesterol:phospholipid molar ratio of 0.8 to 0.9 drastically decreased the intensity of both resonance-enhanced bands. The carotenoid bands in ghosts respond to membrane perturbations. The intensities of the 1530 and 1165 cm(-1) bands are increased by trypsinization, lysolecithin treatment, and reduction of pH. In contrast, a decrease in the intensity of both bands follows equilibration of ghosts for 15 min at about 50 C or addition of (0.1%) sodium dodecyl sulfate. It

is suggested that perturbants known to change lipid-protein interactions in RBC membranes modify the microenvironment and/or configuration of the membrane-bound carotenoid.

18. THE STRUCTURE AND THERMOTROPISM OF THYMOCYTE PLASMA MEMBRANES AS REVEALED BY LASER-RAMAN SPECTROSCOPY.

Verma SP, Wallach DF, Schmidt-Ullrich R
New England Medical Center Hosp., 171 Harrison Ave., Boston, Mass. 02111
Biochim Biophys Acta; 394:633-645 1975

Plasma membranes from rabbit thymocytes were analyzed by laser-Raman spectroscopy over the 800-3000 cm-1 region and the spectra compared with those of endoplasmic reticulum, as well as relevant *liposome systems*. Evaluation of the Amide I and Amide III regions indicated that thymocyte plasma membranes, but not endoplasmic reticulum, contained appreciable beta-structure peptide. This was supported by infrared spectroscopy. Evaluation of the 2890 cm-1 intensity ratio of plasma membranes as a function of temperature using an integration technique, demonstrated a thermotropic lipid transition centered near 23 C, which is less sharp than one observed with egg lecithin in this temperature range. The significance of the thermotropic transition is evaluated in view of the lack of thermotropic lipid-protein segregation detectable by freeze-fracture electron microscopy.

19. RAMAN SPECTROSCOPY OF NORMAL AND ROUS-TRANSFORMED CELL MEMBRANES (MEETING ABSTRACT).

Carew EB, Kaufman HW, Robbins PW, Stanley HE
Dept. Biology, Massachusetts Inst. Technology, Cambridge, Mass. 02139
Biophys J; 16(21-part2):106a 1976

Conformational properties of lipids and proteins were characterized by Raman spectroscopy. Raman spectra of plasma membrane vesicles (PMV) and endoplasmic reticulum vesicles (ERV) obtained from tissue-cultured chick embryo fibroblasts were interpreted in terms of their lipid and protein constituents. A first set of peaks at 1062, 1089, and 1128 cm(-1) , the relative intensities of which were shown in *model lipid vesicles* to vary with the temperature-dependent order-disorder transition, were apparent in spectra of all vesicle preparations. The I1089 /I1130 ratio for PMV was on the order of unity, while it is considerably larger than unity for ERV. PMV obtained from fibroblasts that were tumorigenically transformed by Rous sarcoma virus or pseudotransformed with trypsin had I1089 /I1130 ratios similar to ERV of normal cells. A second set of peaks at 1238, 1268, and 1302 cm(-1) , which were partly or totally shifted on deuteration (H**n to D**n exchange), were interpreted as amide III modes; two peaks (1268 and 1302 cm(-1)) fell within the alpha-helical range, while the third (1238 cm(-1)) was in the beta plate or "random" coil structure region.

B.

Liposome damage due to oxidation and radiation

20. LIPID OXIDATION IN BIOLOGICAL MEMBRANES: ELECTRON TRANSFER PROTEINS AS INITIATORS OF LIPID AUTOXIDATION.

Kaschnitz RM, Hatefi Y
Austrian Academy Sci., Wasagasse 9, A-1090 Vienna, Austria
Arch Biochem Biophys; 171(1):292-304 1975

Liposomes from soybean phospholipids (asolectin) were used as a model test system to comparatively study a large number of membrane electron transfer proteins (hematin, microperoxidase, methemoglobin, cytochrome c, cytochrome c purified, horseradish peroxidase, myoglobin, hemoglobin, cytochrome P450, cytochrome c reduced, and protoporphyrin IX. The role of the superoxide anion was also studied in the autoxidation reactions of the asolectin model. Heme compounds, flavoproteins, and iron-sulfur proteins were examined for their ability to initiate lipid autoxidation. The most active heme compounds were hematin, microperoxidase, methemoglobin and cytochrome c, respectively. With fresh preparations of phospholipids, reaction rates (nanomoles of oxygen/min x nmoles of heme) ranged from 5 (cytochrome c) to 350 (hematin). Only the oxidized heme compounds were active as catalysts. Reduced heme compounds, flavoproteins and riboflavin were inactive. In the presence of heme compounds, aged preparations of sonicated phospholipids were much more rapidly oxidized than fresh preparations. They also had a higher content of fatty acid hydroperoxides. This observation agrees with the postulated mechanism of lipid autoxidation by heme compounds: homolytic scission of preformed fatty acid hydroperoxides. Iron-sulfur proteins were also active as initiators of lipid autoxidation when destabilized in the presence of an appropriate iron chelator (o-phenanthroline or 2,2'-bipyridine) or a chaotropic ion. Oxygen uptake rates (nmoles of oxygen/min x mg of protein) varied from about 200 for an iron-sulfur protein isolated from complex I to about 5500 for Clostridium pasteurianum ferridoxin. However, per nmole of labile sulfide, the rates for all active iron-sulfur proteins were 4-7 nmole oxygen/min x nmole of labile sulfide. Superoxide-generating systems did not initiate lipid autoxidation, nor did erythrocuprein inhibit the autoxidations induced by heme compounds or ferridoxin. However, lipid oxidations induced by two other iron-sulfur proteins were partially inhibited by erythrocuprein. It is concluded that in the above system superoxide anion is neither an initiator nor an obligatory intermediate of lipid autoxidation.

21. EFFECTS OF PHOTODYNAMIC ACTION ON BIOLOGICAL MEMBRANES (MEETING ABSTRACT).

Cohn GE, Collins JM, Clark JE
Physics Dept., Illinois Inst. Technology, Chicago, IL, 60616
Biophys J; 25(2,part2):292a 1979

Photodynamic irradiation with visible light in the presence of eosin Y modifies the properties of lipid regions of yeast cells while inactivating the cells. When the Saccharomyces cerevisiae strain Y55 was inactivated and spin labeled with the fatty acid probe 12NS, electron spin resonance spectra showed that the labels divided into two populations which appeared to correspond to a polar and hydrocarbon location while only the hydrocarbon signal appeared before irradiation. Upon addition of 1.0 M NiCl2 following irradiation, the polar signal was quenched and the hydrocarbon component was left intact. Spin reduction occurred irreversibly for unirradiated Y55 if the temperature exceeded 30 C. For inactivated Y55 the polar signal was predominant at 0 C, but above 30 C the hydrocarbon component was predominant both with and without NiCl2. No spin reduction occurred for inactivated cells at temperatures from 0 C up to 40 C.

Cells labeled with the hydrocarbon probe 7N14 showed no polar contribution to the spectrum either before or after irradiation, nor was rapid spin reduction observed in either case over the same temperature range. A steady increase in spin label tumbling time tau0 was observed when asolectin liposomes were photodynamically irradiated and labeled with the methyl ester of 12NS. Tau0 varied from 1.5 ns initially to 3 ns after treatment but all spectra had hyperfine splittings characteristic of a non-polar environment suggesting damage to the lipid bilayer. These data indicate that eosin-sensitized photodynamic irradiation significantly alters the physical properties and function of membrane regions. (no Refs)

22. LYSIS OF PHOSPHOLIPID MEMBRANES WITH RADIATION-INDUCED FREE RADICALS (MEETING ABSTRACT).

Kalkwarf DR, Frasco DL
Battelle, Pacific Northwest Lab., Richland, WA 99352
Radiat Res; 70(3): 647 1977

Vesicles bounded by a single-bilayer membrane of certain phospholipids and held in aqueous suspension were found to be lysed by several radiation-induced radicals. The vesicles were prepared by sonication to contain a 0.1 M aqueous solution of sodium fluoride buffered with sodium phosphate at pH 7.4, and lysis was followed by measuring the fluoride ion released into the external solution with a selective F-ion electrode. The extent of lysis was found to depend on radical type and number as well as on the polar end group of the phospholipid and the vesicle concentration. The presence of unsaturated fatty-acid residues in the lipid had no observable effect. Significant lysis occurred when vesicle membranes composed of phospholipids with net-neutral polar end groups were exposed to hydroxyl radicals formed by gamma-radiolysis of the suspensions or to radicals released when preirradiated crystals of glycine or galactose were dissolved in the suspensions. In such cases, the decomposition yield increased linearly with vesicle concentration and attained values of up to 0.0006 vesicles lysed per radical added when the vesicle concentration was 5 microM. Very little lysis occurred when vesicle membranes composed of phospholipids with negatively-charged end groups, eg phosphatidylserine and phosphatidylethanolamine, were exposed to similar amounts of radicals. Similarly, negligible lysis was observed when vesicles were exposed to radicals released from pre-irradiated crystals of serine and DL-alpha-alanine during dissolution. (no Refs)

23. RADIATION-INDUCED LIPID PEROXIDATION AND MEMBRANE PERMEABILITY IN LIPOSOMES.

Nakazawa T, Nagatsuka S
Div. Biology, Natl. Inst. Radiological Sciences, 4-9-1, Anagawa, Chiba 260, Japan
Int J Radiat Biol; 38(5):537-544 1980

Effects of 60Co-gamma-ray on liposomal membranes were studied in terms of the correlation between lipid peroxidation and glucose efflux. Malondialdehyde (MDA) formation in glucose-retaining liposomes after gamma-irradiation was highly correlated with the increase in glucose efflux. The MDA formation, however, occurred only during irradiation in contrast to the glucose efflux which continued after irradiation. Both processes showed a dose threshold and a dependence on dose rate. A one-to-one relationship between glucose efflux and MDA formation was observed with radical scavengers. These results are discussed as a series of processes in membrane damage by ionizing radiation. (Author abstract) (24 Refs)

24. INHIBITION BY BISCOCLAURINE ALKALOID OF LIPID PEROXIDATION IN BIOLOGICAL MEMBRANES.

Shiraishi N, Arima T, Aono K, Inoure B, Morimoto Y, Utsumi K
Dept. Medical Biology, Kochi Medical Sch., Kochi 781-51, Japan
Physiol Chem Phys; 12(4):299-305 1980

The action of the bisoclaurine alkaloid cepharanthine (CR) on lipid peroxidation and maintenance of membrane functions was studied in rat liver mitochondrial and microsomal membranes and in phosphatidylcholine liposomes. CR protected the membranes from Fe++-induced lipid peroxidation and prevented the decrease in membrane fluidity and the release of K+ caused by lipid peroxidation. The inhibitory effect of the agent was stronger than that of alpha-tocopherol or coenzyme Q. Of the various CR derivatives examined, a bisoclaurine compound with a diether bond was the most effective in inhibiting the Fe++-induced lipid peroxidation. Claurine-type alkaloids were weak inhibitors. These observations indicated that the protective action of CR against radiation injury may also be due to its effect on lipid peroxidation. (21 Refs)

25. PROTECTION OF LIPOSOMAL LIPIDS AGAINST RADIATION INDUCED OXIDATIVE DAMAGE.

Konings AW, Damen J, Trieling WB
Lab. Radiopathology, Univ. Groningen, Bloemsingel 1, Netherlands
Int J Radiat Biol; 35(4):343-350 1979

Liposomes were prepared from phospholipids extracted from biological membranes. A comparison was made between the peroxidation rate in handshake liposomes and in sonicated liposomes. The smaller sonicated liposomes were more vulnerable to peroxidation, probably because of the smaller radius of curvature, which results in a less dense packing of lipid molecules in the bilayer and a facilitated action of water radicals produced by the x-irradiation. High oxygen enhancement ratios were obtained, especially at low dose rates, suggesting the operation of slowly progressing chain reactions initiated by ionizing radiation. Three compounds were tested for their ability to protect the liposomal membranes against lipid peroxidation. The naturally occurring compounds reduced glutathione (GSH) and vitamin E (alpha-T) and the powerful radiation protector cysteamine (MEA). All three molecules could protect the liposomes against peroxidation. The membrane-soluble compound vitamin E was by far the most powerful. About 50% protection was achieved by using 5 x 10(-6)M alpha-T, 10(-4)M GSH and 5 x 10(-4)M MEA. The fatty acid composition of the lipids was altered drastically as a result of the irradiation. Arachidonic acid was the most vulnerable of the fatty acids. Very efficient protection of these polyunsaturated fatty acids could be obtained with relatively low concentrations of vitamin E built into the membranes. (Author abstract) (28 Refs)

26. PROTECTIVE MECHANISM AGAINST RADIATION DAMAGE OF LIPIDS IN BIOMEMBRANES (MEETING ABSTRACT).

Schutte H, Konings AW
Lab. Radiopathology, Bloemsingel 1, Univ. Groningen, Groningen, Netherlands
14th Annual Meeting of the European Society of Radiation Biology held in Julich, W. Germany, 9-13 October 1978 113 pp., 1978.

We prepared aqueous lipid dispersions of molecules structured as bilayers, a situation also found in biomembranes. These liposomes consisted of phospholipids extracted from biological membranes and prepared in the presence or ab-

sence of the naturally occurring compounds reduced glutathione (GSH) and alpha-tocopherol (alpha-T, Vitamin E) and also in the presence of the well known radiation protector mercaptoethanolamine (MEA, cysteamine). As an indicator for lipid peroxidation in the liposomes, the formation of conjugated dienes was measured and the change in the fatty acid pattern as a result of the irradiation was determined. Destruction of polyunsaturated fatty acids (PUFA) was demonstrated and appeared to be oxygen and dose rate dependent. More severe damage was done to the PUFA at low dose rates. The concentrations which yielded about 50% protection against lipid peroxidation were 4 x 10(-6) M alpha-T, 1 x 10(-4) M GSH and 5 x 10(-4) M MEA. The fatty acid composition of the lipids altered drastically as a result of the irradiation, arachidonic acid (20:4) and docosahexaenoic acid (22:6) being the most vulnerable species. Very effective protection of these PUFA could be obtained with relatively low concentrations of vitamin E built into the membranes. vitamin E itself was oxidized during the irradiation process in the liposomes. Mice were injected with tritium labeled alpha-T. The effect of irradiation on the radioactive alpha-T content in vivo in the different subcellular fractions of the liver revealed that the cell nuclei had a drastically reduced level of this vitamin. Injection of cysteamine prior to irradiation could prevent the observed loss of alpha-T in the nuclei. PUFA in biomembranes may be directly protected by vitamin E because of the structural properties of this compound, while water soluble anti-oxidants take part in a secondary protective system, keeping vitamin E in a reduced state. (no Refs)

27. OXIDATIVE DAMAGE TO MEMBRANE LIPIDS BY IONIZING RADIATION AND PROTECTION BY VITAMIN E (MEETING ABSTRACT).

Schutte HH, Konings AW
Lab. Radiopathology, Univ. Groningen, Groningen, The Netherlands
Int J Radiat Biol; 34(6):551 1978

Physical agents such as ionizing radiation enhance free-radical reactions in living cells and may destroy control processes normally functioning in protecting biological membranes against lipid oxidation. *Liposomes* are aqueous lipid dispersions of molecules structured as bilayers, a situation also found in biomembranes. In this study phospholipids were used which were extracted from biomembranes and prepared in the presence or absence of protecting substances. Irradiation with x-rays was performed at different dose rates under oxic and hypoxic conditions. Conjugated dienes as well as fatty acid composition were measured. Destruction of polyunsaturated fatty acids appeared to be oxygen-dependent and more severe at lower dose-rates. Small liposomes were more vulnerable, presumably because of the reduced radius of curvature in these vesicles, resulting in a better attainability of the radiation-induced water radicals to the unsaturated fatty acids in the bilayer. Vitamin E appeared to be at least 100 x more efficient in protecting against fatty acid oxidation as compared to the water soluble compound cysteamine. Vitamin E was oxidized during the irradiation process. Arachidonic acid (20:4) and docosahexenoic acid (22:6) were particularly well protected by vitamin E. The relevance of these results for the in vivo situation will be discussed. (no Refs)

28. EFFECT OF RETINOL ON PEROXIDE OXIDATION IN PHOSPHOLIPID MEMBRANES.

Deev AI, Eremina TV, Spirichev VB
Inst. Nutrition, Moscow, USSR
Vopr Med Khim; 24(6):795-798 1978

The effect of retinol on the kinetics of peroxide oxidation was studied in phospholipid membranes isolated from egg yolks. Incubation of liposomes with retinol was found to change the kinetics of lipoperoxidation. The effect depended upon the concentration of retinol: at 0.15 M retinol enhanced the peroxide oxidation, while at 1.0 M retinol had a marked antioxidative effect. (19 Refs)

III. INTERACTIONS OF VARIOUS SUBSTANCES WITH LIPOSOMES

A.

Entrapment of antitumor agents in liposomes

29. THE IN VITRO AND IN VIVO STABILITY OF THE ENTRAPMENT OF METHOTREXATE IN NEGATIVELY CHARGED LIPOSOMES AFTER STERILE FILTRATION.

Freise J, Magerstedt P, Schmidt FW
Abteilung fur Gastroenterologie und Hepatologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, W. Germany
Z Naturforsch [C]; 34(1/2):114-119 1979

The preparation, sterilization, and storage stability of methotrexate (MTX) entrapped in artifically prepared liposomes were studied in order to produce MTX-containing liposomes (MTX-L) stable for at least 1 mo. Previously prepared liposome-drug complexes were stable for only a few days, which is not satisfactory for many therapeutic applications. The negatively-charged MTX-L were prepared using phosphatidylcholine:cholesterol:diacetylphosphate in the molar ratio of 5:5:1 and adding MTX + [3H]MTX in sodium phosphate buffer (NPB), pH 7.3. Rotation and ultrasonic waves were used to form lipid vesicles around the MTX. The MTX-L were then thermostabilized at 65 C, and free MTX was separated from the MTX-L by chromatography on Sepharose 6B. MTX encapsulation, as measured in the chromatographed material, was 170 +/-60 ug/ml if 5 milliM NPB was used, but only 140 +/-35 ug/ml if 50 milliM NPB was used. Filtration through a millipore filter (0.22 mum) produced sterile preparations and did not release detectable amounts of MTX from the MTX-L. The storage stability of MTX-L was better at 4 C than at 20 C. The use of 50 milliM NPB or of 5 milliM NPB + bovine albumin, mouse serum, or human serum gave MTX-L stability for 120 days. No free MTX was detected after chromatography of plasma from mice 15 hr after the injection of MTX-L, indicating that the MTX was stable for at least this long. At 15 hr, 3% of the injected MTX-L dose was found in the plasma. This method for preparing MTX-L should allow further study of uses for liposome-entrapped drugs. (13 Refs)

30. INTERACTION OF ANTICANCER AGENTS WITH CARRIERS FACILITATING CELLULAR UPTAKE.

Chen ST
Purdue Univ., Lafayette, IN

Diss Abstr Int [B]; 39(2):668B-669B 1978

The physical-chemical characteristics of the interaction between the anticancer agents methotrexate (MTX) and 6-mercaptopurine riboside 5'-phosphate (MPRP) and the polycations diethylaminoethanol (DEAE)-dextran and poly-L-lysine were studied. Three different methods, equilibrium dialysis, dynamic dialysis, and difference spectroscopy were employed to evaluate the binding and thermodynamic parameters of the binding process. The drug-polycation interaction is mainly governed by nonspecific electrostatic forces between drug anions and polycations. The binding of MTX with both DEAE-dextran and poly-L-lysine acetate is an exothermic reaction, whereas the binding of MPRP with the same polycations is a temperature independent reaction. The fraction of bound drug in the polycation soln is dramatically influenced by ionic strength. The polymeric structure of the polycation, as well as conformational changes, may play a significant role in the binding process. Following a 1 hr incubation of MPRP (which was previously bound to poly-L-lysine) in 0.02 M acetate buffer (pH 7.40) the compound was dissociated completely when the ionic strength was raised to 0.15. However, after a 3-day incubation period in 0.02 M acetate buffer (pH 7.40), there was no dissociation of bound MPRP when the ionic strength was increased to 0.15. A time dependent difference spectrum for 6-MPRP-poly-L-lysine acetate soln was observed. This indicated a conformational change in the poly-L-lysine with a subsequent change in the affinity of the polymer for MPRP. Human serum albumin did not have an effect on the fraction of bound MTX in either DEAE-dextran and poly-L-lysine acetate systems. The effect of several physical-chemical properties of *MTX liposomes* and operational variables on the extent of entrapment and rate of diffusional loss of drug from liposomes were studied. The percentage entrapment was independent of the various kinds of phospholipid, but dependent upon the lipid-aqueous phase ratios. Swelling time and sonication time should be well-controlled to obtain max percentage entrapment. Increasing the molar ratio of cholesterol to sphingomyelin decreased the rate of diffusion of entrapped MTX from the liposomes. No temperature effect was observed for MTX-containing sphingomyelin liposomes when the temperature was increased from 22 C to 37 C. Human serum albumin did not affect the permeability of negatively charged sphingomyelin liposomes. (no Refs)

31. IMPROVED ENTRAPMENT OF DRUGS IN MODIFIED LIPOSOMES.

Tsujii K, Sunamoto J, Fendler JH
Dept. Chemistry, Texas A and M Univ., College Station, TX 77843

Lif Sci; 19(11):1743-1750 1976

Enhancement of drug encapsulation by charge transfer complexation was reported. The electron donors were 8-azaguanine (AG) and 6-mercaptopurine (6-MP). Chloranil (CA), 3,5-dinitrobenzoyl-n-butylamine (DNBBA), and 3,5-dinitrobenzoyl phosphatidylethanolamide (DNBPE) were used as the electron acceptors. Calculation of the number of drug molecules per dipalmitoyl-DL-alpha-phosphatidylcholine liposome was based on the assumption that the external diameter of single compartment liposomes is about 250 A and that each such liposome contains 3,000 phospholipid molecules. The number of vesicles per micromole of phospholipid was then computed to be 2 x 10(14). DNBBA and DNBPE did not appreciably enhance incorporation of AG or 6-MP at any pH between 6.0 and 10.0. At pH 7.0, CA potentiated 6-MP entrapment from 0.18% to 30-32%, at pH 8.0 from 0.1% to 15%, and at pH 6.0 from 0.45% to 27%; entrapment was not as significant at higher pH. AG entrapment was also improved by CA at pH 6.0 from 0.86% to 5.7%. The enhancement is attributable to charge transfer, whose complexes are also unstable. (29 refs)

32. INTERACTIONS OF DRUGS WITH LIPID MEMBRANES. CHARACTERISTICS OF LIPOSOMES CONTAINING POLAR OR NON-POLAR ANTITUMOR DRUGS.

Juliano RL, Stamp D
Res. Inst., Hosp. Sick Children, 555 Univ. Ave., Toronto, Ontario, Canada

Biochim Biophys Acta; 586(1):137-145 1979

Polar drugs entrapped within liposomes are found in the internal aqueous compartments of these particles, and are readily released when the liposome membrane is ruptured by ultrasonic energy. Nonpolar drugs are bound or intercalated into the liposome membrane as well as being found in the aqueous compartments. The intercalated fraction of the nonpolar drug is relatively refractory to release by ultrasonic energy. The efflux rates of both polar and nonpolar drugs from liposomes are governed by the physical characteristics of the liposome membrane. Thus drug efflux from liposomes composed of synthetic phosphatidylcholines displays a max rate at the phase transition temperature of the lipid. The efflux rate of nonpolar drugs from phosphatidylcholine liposomes is greater than that of polar drugs. Nonpolar drugs can perturb the phase transition behavior of synthetic phosphatidylcholines; polar drugs have no such effect. Thus, in the presence of nonpolar drugs such as vinblastine sulfate and actinomycin D, the differential scanning calorimetry profile of dimyristoylphosphatidylcholine is markedly altered, with a broadening of the major peak and the appearance of a second peak at lower temperature. (Author abstract) (16 Refs)

33. A DIFFERENTIAL INTERACTION OF DAUNOMYCIN, ADRIAMYCIN AND THEIR DERIVATIVES WITH HUMAN ERYTHROCYTES AND PHOSPHOLIPID BILAYERS.

Goldman R, Facchinetti T, Bach D, Raz A, Shinitzky M
Dept. Membrane Res., Weizmann Inst. Science, Rehovot, Israel

Biochim Biophys Acta; 512(2):254-269 1978

Drug-membrane association of daunomycin, adriamycin and three of its derivatives, adriamycin-14-octanoate (AD-14-OCTA), adriamycin-14-acetate (AD-14-ACE) and N-trifluoroacetyladriamycin-14-valerate (AD32), was studied using phospholipid bilayers and human RBC. The various drugs exhibited a differential affinity to membrane-lipid domains. Lipid-incorporated drugs exhibit a marked change in the shape of the emission spectrum which was utilized for the evaluation of the apparent dielectric constant, epsilon, of the environment surrounding the anthracycline moiety, as well as for the determination of the partitioning constant. By measuring the fluorescence polarization and the fluorescence lifetime of the incorporated drugs, rotational relaxation times of 4-8 ns were derived. These parameters provide a supportive evidence for the association of the fluorophore of the drugs with membrane-lipid domains. The anthracycline derivatives interact to a different degree with dipalmitoyl phosphatidylcholine and phosphatidylserine as reflected by changes in their thermotropic properties assessed by differential scanning calorimetry. Daunomycin was the most effective in decreasing the temperature of the phase transition and brought about a comparable reduction in the

enthalpy of melting as AD32 and AD-14-OCTA. Adriamycin was the least potent of the series. AD-14-ACE and AD32 protected RBC against hypotonic lysis, adriamycin and daunomycin had no significant effect on the susceptibility to hypotonic lysis, whereas AD-14-OCTA proved to be hemolytic even at low concentration (approx 10(-7) M). (Author abstract) (35 Refs)

34. EFFECTS OF ADRIAMYCIN ON LIPOSOMAL AND CELLULAR MEMBRANE STUDIES BY MAGNETIC RESONANCE (MEETING ABSTRACT).

Murphree SA, Tritton TR
Dept. Pharmacology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Fed Proc; 38(3,part1):258 1979

We have observed that adriamycin (Adr) has a unique effect on fluidity of liposomes (LS) containing small amounts of cardiolipin (CL). Nuclear magnetic resonance spectroscopy was used to measure fusion rates and permeability characteristics of dimyristoyl phosphatidyl choline (DMPC) LS containing small amounts of other lipids. LS (30 mg/ml) of DMPC alone, or with Adr (10-4M) at a molar ratio of 100:1, showed little or no fusion (t1/2 = 277 hr). Addition of 0.5 mole% CL to LS enhanced the rate of fusion (t 1/2 = 146 hr) and exposure to Adr further increased the rate (t 1/2 = 42.5 hr). Other lipids added to DMPC at 0.5 mole% in the presence of Adr gave t 1/2 values of 222 hr, phosphatidylserine; 334 hr, sphingomyelin; 46 hr, stearylamine; and 74 hr, phosphatidylglycerol. Addition of Ca++ (1 milliM (mM)) to LS did not affect fusion, but Adr and Ca++ enhanced fusion of all lipids tested, with CL-containing LS having the fastest rate (t 1/2 = 17.6 hr). Permeability of liposomal membranes, measured by distribution of the paramagnetic ion Pr+3, was not affected by addition of Adr or Ca++ to LS of DMPC or DMPC and CL, suggesting maintenance of membrane integrity. Use of 5-deoxylstearic acid as a spin label with cultured Sarcoma 180 cells suggest that Adr increases fluidity of cell membranes; that is, the order parameter decreased from 0.627 to 0.608 at 37 C. Results support an action by Adr on membranes. (no Refs)

35. ADRIAMYCIN: A PROPOSAL ON THE SPECIFICITY OF DRUG ACTION.

Tritton TR, Murphree SA, Sartorelli AC
Dept. Pharmacology, Comprehensive Cancer Center, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Biochem Biophys Res Commun; 84(3):802-808 1978

Transition temperatures (Tm) from gel to liquid crystal were studied in dipalmitoyl lecithin (DPL) *liposomes* containing small amounts (1%) of other lipids incorporated into the bilayer, in the presence or absence of adriamycin (ADR: 10(-4) M). The addition of ADR to DPL liposomes consistently reduced the Tm by about 1 C. ADR also reduced the Tm of membranes of mixed lipid composition, including those with a net negative surface charge (DPL with bovine phosphatidyl serine) and a net positive surface charge (DPL with stearyl amine) and DPL with bovine sphingomyelin. DPL liposomes containing bovine cardiolipin (diphosphatidyl glycerol) showed an increased Tm in the presence of ADR, showing that ADR reduced the fluidity of this bilayer. This was not a nonspecific effect of an acidic phospholipid, since ADR fluidized DPL liposomes containing phosphatidyl glycerol (half of the cardiolipin molecule) and phosphatidyl serine. Scatchard plots of the equilibrium binding properties of ADR with both dimyristoyl lecithin liposomes and membranes containing cardiolipin were similar. There was no single type of binding site. The limiting affinity constant was about 6 x 10(-3) M. Since the presence of cardiolipin apparently did not create a unique binding site or alter the affinity of the liposomes for ADR, the differential effect of ADR on cardiolipin-containing membranes was attributed to the change in membrane organization occurring in the presence of cardiolipin. Cardiolipin, normally restricted to the mitochondrial membranes, may develop in all cell membranes upon malignant transformation. This dedifferentiation with respect to cardiolipin may be involved in the susceptibility of tumor cells to the anthracyclines, as well as the cardiotoxic effects of these agents. (13 Refs)

36. DIFFERENTIAL EFFECTS OF ADRIAMYCIN ON FLUIDITY AND FUSION CHARACTERISTICS OF CARDIOLIPIN CONTAINING LIPOSOMES. (MEETING ABSTRACT).

Murphree SA, Tritton TR, Sartorelli AC
Dept Pharmacol, Yale Univ Sch Med, New Haven, CT 06510
Fed Proc; 36(3):303 1977

Adriamycin (Adr) at growth inhibitory levels enhances the rate of agglutination of Sarcoma 180 cells by Concanavalin A (Con A) without affecting Con A binding (Murphree et al, Biochem Pharm 25: 1227, 1976). To examine interaction of Adr (10(-4)M) with membrane lipids, we have utilized liposomes (LS) with a lecithin matrix and small amounts of other phospholipids. Using a turbidimetric assay, the characteristic temperature (Tm) of the solid to fluid transition of dipalmitoyl lecithin (DPL) LS was lowered about a degree by Adr. However, exposure of LS containing 1% cardiolipin (CL) to Adr increased the Tm about 1-1.5 degrees. The Tm increase with CL containing LS is apparently not a non-specific effect of acidic phospholipids, since LS containing 1% phosphatidyl serine (PS) exhibited a decreased Tm (1 degrees) in the presence of Adr. CL also differentially affects the fusion of LS as measured by (1)H nuclear magnetic resonance. LS of dimyristoyl lecithin (DML) fuse extremely slowly with no change produced by Adr. When 0.1% CL was present in LS, slow fusion of vesicles occurred and addition of Adr induced very rapid fusion. Addition of Adr to LS of DML containing 0.1% PS induced fusion, but at a rate slower than for LS of DML containing CL. The results suggest that Adr alters fluidity and fusion characteristics of phospholipid vesicles and that a differential effect occurs on CL containing membranes. (Author Abstract)

37. INCORPORATION OF RUBOMYCIN INTO MULTILAYER LIPOSOMES.

Popov GA, Goncharov PI
Dept. Biophysics, Res. Inst. Medical Radiology, Obninsk, USSR
Antibiotiki; 25(5):367-370 1980

Incorporation of antitumor antibiotic rubomycin (RM), into different phases of multilayer liposomes was studied. It was found that the percent of incorporation reached the max of RM:lecithin in 1:10; 70% of RM was incorporated into lipid phase of liposomes, compared with 5% in the aqueous phase. (10 Refs)

38. ACTION OF THE PEPTIDE ANTIBIOTIC LEUCINOSTATIN.

Ishiguro K, Arai T
Div. Chemotherapy, Chiba Cancer Center Inst., Nitona, Chiba, Japan
Antimicrob Agents Chemother; 9(6):893-898 1976

The cytotoxic action of leucinostatin (LEU), an antimicrobial and antitumor antibiotic, against the murine leukemic cell line L1210 was investigated. Complete cell growth inhi-

bition was achieved with 0.5 ug/ml of LEU. In addition, LEU showed membrane damage against L1210 cells as well as mouse RBC. The concentration of LEU required for 50% membrane damage of L1210 cells in phosphate-buffered saline was 25 ug/ml; whereas in Eagle minimum essential medium (MEM), a concentration of 75 ug/ml was required for 50% membrane damage. The protective effect of MEM was identified as glucose. The addition of 2-deoxyglucose (dose not specified) did not result in any protective effect. The protection by a metabolizable sugar, but not by a nonmetabolizable one, can be explained by the assumption that this drug might primarily produce a drain on the energy-yielding system. Experiments with mouse RBC showed that a LEU concentration of 100 ug/ml was capable of producing a 50% release of Hb, regardless of the presence or absence of glucose. A possible involvement of membrane lipid in LEU's mechanism of action was evidenced by the observation that *liposomes* prepared with lecithin, cholesterol, and an amphiphatic molecule (either dicetyl phosphate or stearylamine) were sensitive to LEU. The response to the drug was enhanced as the cholesterol level of liposomes was decreased. Changes in the net charge of the membrane did not significantly affect LEU's action. The addition of 10 ug/ml of LEU to an intact L1210 cell system resulted in protein synthesis inhibition before the detection of membrane damage, with the former occurring as early as 20 min after drug addition and the latter not being found even after 4 hr. No protein synthesis inhibition was observed in a cell-free system. Protein synthesis inhibition in intact cell systems is suggested to occur as a result of the initial interaction of the drug with membrane phospholipid. (16 refs)

39. L-ASPARAGINASE ENTRAPPED IN LIPOSOMES: PREPARATION AND PROPERTIES.

Fishman Y, Citri N
Hebrew Univ., Hadassah Med. Sch., Jerusalem, Israel
FEBS Lett; 60(1):17-20 1975

L-asparaginase was successfully entrapped in liposomes in the presence of aspartic acid and gelatin by shaking with liposomes for 2 hr at room temperature. Enzyme activity of > 12% of the original was retained in the washed liposome preparations. Intact liposomes showed 42% of the activity of the entrapped enzyme, and full activity was recovered after disruption by osmotic shock. The entrapped enzyme had a markedly increased thermal stability; 80% of the activity remained after 3 min at 68 C. The entrapped enzyme was also resistant to proteolysis with trypsin, nor did it react with antibodies prepared against the free enzyme. The antigenic determinants of this enzyme appear to have been completely masked in the entrapped preparation. The in vivo behavior and the therapeutic potential of the asparaginase liposomes in the treatment of leukemia are currently under investigation. (12 refs)

40. INTERACTION OF COLCHICINE WITH PHOSPHATIDYLCHOLINE MEMBRANES.

Alstiel LD, Landsberger FR
Rockefeller Univ., New York, NY 10021
Nature (Lond); 269(5623):70-72 1977

A detailed spin-label study using phosphatidylcholine (PC) liposomes shows that colchicine does not interact with the lipid bilayer of PC, and that colchicine might interact with membrane and/or microtubular protein. Electronic spin resonance spectra and data are presented. (24 Refs)

B.
Protein interactions and incorporation into liposomes

41. LIPOSOMAL FUSION AS A MEANS OF INTRODUCING SURFACE ANTIGENS INTO LIVING CELL MEMBRANES.

Heath TD, Robertson D, Birbeck MS, Davies AJ
Chester Beatty Res. Inst., Inst. Cancer Res., Fulham Road, London SW3 6JB, England
Gan Monogr Cancer Res; 23:255-264 1979

The characteristics of the liposome membranes which make them useful in many kinds of biological experiments are described. Liposomal enzymes closely resemble the phospholipid component of mammalian cell membranes, an effect which can be enhanced when proteins are associated to form proteoliposomes. Proteins may be easily encapsulated within the liposomal membranes or covalently bound to their outside surface. Fusion of liposomes to cells results in the entry of water soluble liposome contents into the cell cytoplasm and opens the possibility of inserting the liposome membrane into cell membrane. Techniques for binding proteins to liposomal membranes and then fusing proteoliposomes to mammalian cells in such a way that the protein component becomes an integral part of the cell membrane are discussed. (43 Refs)

42. RECONSTITUTION OF PURIFIED DETERGENT-SOLUBLE HLA-A AND HLA-B ANTIGENS INTO PHOSPHOLIPID VESICLES.

Engelhard VH, Guild BC, Helenius A, Terhorst C, Strominger JL
Biological Lab., Harvard Univ., Cambridge, MA, 02138
Proc Natl Acad Sci USA; 75(7):3230-3234 1978

Purified detergent-soluble human histocompatibility antigens (HLA-A and HLA-B) were reconstituted into phospholipid vesicles by mixing the protein and lipid together in the presence of either octylglucoside (ocytl-beta-D-glucopyranoside) or deoxycholate and removing the detergent by dialysis. The resulting preparation consisted of lipid vesicles containing all or most of the added protein. The protein in the vesicles was antigenically active, as demonstrated by specific binding to anti-beta2-microglobulin IgG-Sepharose beads and by specific inhibition of alloantibody and complement-mediated cytotoxicity. Protein incorporated into vesicles at a protein/phospholipid ratio of 1:10 showed an asymmetric distribution of the HLA-A and HLA-B molecules, with virtually all of the antigens oriented facing the external medium. Cleavage experiments with proteases showed that the molecule was attached to the vesicle membrane via the COOH terminus, consistent with its proposed structure in intact cellular plasma membranes. Electron micrographs of the vesicles showed 50-60 A knobs on the outer surface similar to structures observed for other membrane proteins. HLA-A and HLA-B could also be incorporated into vesicles together with Semliki Forest virus membrane proteins. The resulting preparations should be useful in defining the molecular interactions involving HLA-A and HLA-B antigens in the immune response. (Author abstract) (27 Refs)

43. INSERTION OF BIOLOGICALLY ACTIVE MEMBRANE PROTEINS FROM RAT LIVER INTO THE PLASMA MEMBRANE OF MOUSE FIBROBLASTS.

Baumann H, Hou E, Doyle D
Dept. Molecular Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263

J Biol Chem; 255(20):10001-10012 1980

Phospholipids, glycolipids, and total proteins were separated from a plasma membrane fraction of rat liver. Membrane glycoproteins were isolated from deoxycholate extracts of rat liver membranes and hepatoma tissue culture membranes by concanavalin A chromatography. The membrane glycoprotein on hepatocytes that acts as a receptor for serum glycoproteins that have lost their terminal sialic acid was also purified from rat liver membranes. Closed membrane vesicles were reconstituted from mixtures of deoxycholate-solubilized phospholipids and proteins by dialysis and purified by isopycnic centrifugation. The orientation of the proteins and glycoproteins in these reconstituted vesicles was examined by their accessibility to trypsin and neuraminidase and by their ability to be released from the vesicle by different concentrations of detergent. Most of the proteins are embedded in a right-side-out orientation in the lipid bilayer. The reconstituted membrane vesicles can be fused to mouse L-cells with polyethylene glycol. The extent of fusion is a function of the phospholipid:protein ratio in the reconstituted vesicles. After fusion, the phospholipid component of the vesicles mixes relatively rapidly with cell membrane lipids as judged by the immunofluorescence pattern of cells fused with lipid vesicles containing trinitrophenylated lipids. In contrast, proteins transferred to L-cells show restricted diffusion as judged again by immunofluorescence techniques. The metabolic turnover of proteins and glycoproteins after transfer to the plasma membranes of mouse L-cells was examined by radioisotopic methods. Total rat liver membrane proteins are very stable after transfer to the L-cells. Some of these proteins may be involved in the formation of an exoskeleton at the cell surface. Hepatoma tissue culture cell glycoproteins after transfer to the L-cells are less stable in terms of turnover properties than are total liver membrane proteins. However, some of these proteins are released into the medium as large mol wt material rather than being degraded to small mol wt, acid-soluble component. The receptor for serum asialoglycoproteins is relatively stable after transfer in reconstituted vesicles to the membrane of L-cells. Most of this hepatocyte-specific membrane glycoprotein is degraded to acid-soluble material with a half-life in the L-cell of at least 50 hr. Transfer of the purified receptor in reconstituted vesicles to L-cells confers upon the recipient cell the biological activities specific and initiated by these receptors in hepatocytes. (Author abstract) (36 Refs)

44. POSITIVE COOPERATIVITY IN A (DISSECTED) LECTIN-MEMBRANE GLYCOPROTEIN BINDING EVENT.

Ketis NV, Girdlestone J, Grant CW
(c/o Girdlestone) Dept. Biology, Univ. Oregon, Eugene, OR, 97201

Proc Natl Acad Sci USA; 77(7):3788-3790 1980

A transmembrane glycoprotein, glycophorin, was assembled into large liposomes that may be handled like intact cells. Under appropriate conditions, lectin binding to these simple model cells accurately mimics the positive cooperative behavior commonly reported for binding of various lectins to real cells. Hence we suggest that the simple observation of cooperativity in such a cell-surface recognition event does not necessarily imply an involvement of complex cellular machinery; rather, it may simply reflect interaction of a multivalent ligand with conformationally deformable headgroups. (Author abstract) (23 Refs)

45. ASSOCIATION OF GROSS VIRUS-ASSOCIATED CELL-SURFACE ANTIGEN WITH LIPOSOMES.

Sakai F, Gerlier D, Dore JF
Laboratoire d'Immunologie et de Cancerologie Experimentale, INSERM FRA NO. 24, 69373 Lyon Cedex 2, France

Br J Cancer; 41(2):227-235 1980

Gross cell-surface antigen (GCSAa) was obtained from W/Fu (C58NT)D lymphoma cells by Nonidet P40 (NP40) or 3 M KCl extraction and further purified by Sephadex G200 filtration. GCSAa was associated with lipids (dipalmitoylphosphatidycholine, cholesterol and dicetylphosphate, in M ratios of 7:2:1) to form multilamellar liposomes. The amount of protein associated with liposomes was found to be proportional to the protein concentration of the sensitizing cellular extract and to the amount of phospholipids used and, under defined conditions, 22-55% of the protein of the cellular extract could be associated with liposomes. Analysis of disrupted sensitized liposomes showed that the GCSAa-specific activity of the liposome-associated proteins was quite similar to that of the proteins of the sensitizing cellular extract. Ultracentrifugation of disrupted liposomes showed that about 75% of the liposome-associated GCSAa activity was firmly associated with lipids and that little GCSAa was trapped within aqueous compartments between lipidic lamellae. 1.8-8.0% of the liposome-associated GCSAa was expressed at the liposome surface. No striking differences in degree of GCSAa association were found between liposomes sensitized by NP40 or by 3 M KCl extracts. Storage experiments at +4 C showed that GCSAa-sensitized liposomes were fairly stable. (Author abstract) (26 Refs)

46. ISOLATION OF A CELL-SURFACE ANTIGEN ASSOCIATED WITH GROSS VIRUS IN LIPOSOMES.

Gerlier D, Sakai F, Dore JF
Laboratoire d'Immunologie, Centre Leon-Berard, 28, rue Laennec, 69373 Lyon Cedex 2, France

C R Acad Sci [D] (Paris); 286(5):439-442 1978

A Gross virus-associated cell-surface antigen was extracted from (C58NT)D lymphoma cells by detergent solubilization of the membranes and then partially purified. Absorption experiments, in which the cytotoxicity of W/Fu rat anti-(C58NT)D serum toward E(male)G2 lymphoma cells was determined, indicated that the antigen was located on the surface of sensitized liposomes. (13 Refs)

47. RECONSTITUTION OF THE HEPATIC ASIALOGLYCOPROTEIN RECEPTOR WITH PHOSPHOLIPID VESICLES.

Klausner RD, Bridges K, Tsunoo H, Blumenthal R, Weinstein JN, Ashwell G
(c/o Ashwell), NIH, Building 10, Room 9N-119 LBM, NIAMDD, Bethesda, MD, 20205

Proc Natl Acad Sci USA; 77(9):5087-5091 1980

A solubilized detergent-free preparation of the hepatic binding protein specific for asialoglycoproteins associates spontaneously with small unilamellar lipid vesicles. This process is independent of the phase transition of the lipid and effectively restores the specific binding activity of the receptor protein. The insensitivity of the resulting lipid-protein complex to ionic strength provides evidence for a hydrophobic interaction. There is a perturbation of the lipid phase transition concomitant with addition of the protein. Circular dichroism studies indicate that the protein undergoes a con-

formational change on association with lipid. Binding of specific ligand produces further physical changes in the receptor as indicated by alterations in the tryptophan fluorescence quenching pattern. (Author abstract) (12 Refs)

48. EFFECT OF PHOSPHATIDYLCHOLINE VESICLES ON THE ACTIVITY OF DNA POLYMERASE-ALPHA.
Capitani S, Mazzotti G, Jovine R, Papa S, Maraldi NM, Manzoli FA
Instituti de Anatomia Umana Normale, Universita di Bologna e Chieti, Bologna, Italy
Mol Cell Biochem; 27(3):135-138 1979

Phosphatidylcholine vesicles stimulate the activity of the DNA polymerase-alpha from calf thymus. This effect is dependent upon the way of addition of the Mg ions, and the extent of the 3H-deoxythymidine triphosphate incorporation is closely related to the concentration of the vesicles. A role of phospholipids on the activity of the DNA-related enzymes is suggested. (Author abstract) (24 Refs)

49. PROTEIN-LIPOSOME INTERACTIONS AND THEIR RELEVANCE TO THE STRUCTURE AND FUNCTION OF CELL MEMBRANES.
Kimelberg HK
Albany Medical Coll. Union Univ., Albany, NY 12208
Mol Cell Biochem; 10(3):171-190 1976

Recent studies on the interactions of soluble proteins, membrane proteins and enzymes with phospholipid model membranes are reviewed. Similarities between the properties of such systems and the behavior of biomembranes, such as alterations in the redox potential of cytochrome c after binding to membranes, and effects of phospholipid fluidity on (Na+/K+)ATPase activity, are emphasized. The degree of correspondence between the model systems and natural membranes encourages continuing use of model membranes in studies on protein-lipid interactions. However, some of the data on the increase of surface pressure of phospholipid monolayers by proteins and on increases in the permeability of liposomes, indicate that many soluble proteins are also able to interact hydrophobically with phospholipids. Thus, a sharp distinction between both peripheral and integral membrane proteins and non-membrane proteins is not seen by these techniques. Also discussed are studies implicating protein-lipid interactions and (Na+/K+)ATPase activity in membrane alterations.

50. PURIFIED NADPH CYTOCHROME P-450 REDUCTASE. INTERACTION WITH HEPATIC MICROSOMES AND PHOSPHOLIPID VESICLES.
Gum JR, Strobel HW
Dept. Biochemistry, Molecular Biology, Univ. Texas Medical Sch. at Houston, Houston, TX, 77025
J Biol Chem; 254(10):4177-4185 1979

Homogeneous detergent-solubilized NADPH-cytochrome P-450 reductase but not steapsin-solubilized cytochrome c reductase was incorporated spontaneously into microsomes, microsomes treated with steapsin-protease to remove endogenous reductase, and synthetic phospholipid vesicles. This incorporated reductase was active in electron transfer to cytochrome P-450, as shown by its participation in the NADPH-dependent demethylation of benzphetamine. Microsome- and vesicle-bound reductase was not removed by washing in high salt buffers, indicating hydrophobic binding forces. Detergent-solubilized reductase was stabilized against heat denaturation by Renex 690 and phospholipid vesicles, and appeared to aggregate in the absence of detergent; however, no such protective effects or aggregation were observed with the steapsin-solubilized reductase. Treatment of detergent-solubilized reductase vesicle complexes with steapsin protease released cytochrome c reductase activity from the vesicles and converted the protein to a form with the electrophoretic mobility of the steapsin protease-solubilized enzyme and a 12,500-dalton fragment. These results and the ability of phospholipid vesicles to protect the 12,500-dalton fragment against further proteolysis indicate that detergent-solubilized reductase contains a separable membrane binding domain, at least part of which is intercalated directly into the hydrophobic core of the phospholipid bilayer. The amino acid composition of the membrane binding domain, calculated as the difference between detergent-solubilized reductase and steapsin-solubilized reductase, was not especially hydrophobic, but did contain 32.9% asparagine and glutamine, which may indicate that only a portion of the membrane binding domain is enmeshed in the hydrophobic core of the membrane. (Author abstract) (69 Refs)

51. INCORPORATION OF NADPH-CYTOCHROME P-450 REDUCTASE INTO MICROSOMES AND LIPOSOMES (MEETING ABSTRACT).
Gum JR, Strobel HW
Univ. Texas Medical Sch., Houston, TX, 77025
Fed Proc; 37(3):425 1978

NADPH-cytochrome P-450 reductase (DSR) prepared by detergent solubilization and affinity chromatography is incorporated into rat liver microsomes as judged by a 4-to 5-fold increase in the specific activity of microsomal cytochrome c reduction after incubation with DSR and collection of the twice-washed microsomes. However, incubation of microsomes with steapsin-solubilized NADPH-cytochrome c reductase (SSR) under similar conditions results in no significant increase in cytochrome c reductase specific activity. DSR also incorporates into artificial phospholipid vesicles. Incubation at 37 C for 30 min of 6.0 microM DSR with egg yolk phosphatidylcholine resulted in the binding of at least 60% of the NADPH-cytochrome c reductase activity to vesicles as judged by ultracentrifugation or Sepharose 4B chromatography. Incubation at 4 C for 24 hr of 8.0 microM DSR with 90% dipalmitoyl phosphatidylcholine-10% dipalmitoyl phosphatidylethanolamine vesicles resulted in the incorporation of at least 68% of the DSR into vesicles. SSR was not incorporated into vesicles under these conditions. Upon incubation of DSR-containing vesicles with steapsin, a fragment with the electrophoretic mobility of SSR was generated. These data support the conclusion that NADPH-cytochrome P-450 reductase contains a membrane-binding domain which can be removed by limited proteolysis and is capable of spontaneously binding to lipid bilayers.

52. IDENTIFICATION AND TRANSMEMBRANOUS LOCALIZATION OF ACTIVE CYTOCHROME OXIDASE IN RECONSTITUTED MEMBRANES OF PURIFIED PHOSPHOLIPIDS BY ELECTRON MICROSCOPY.
Ruben GC, Telford JN, Carrol RC
Section Applied Physics, Cornell Univ., Ithaca, NY 14853
J Cell Biol; 68(3):724-739 1976

Cytochrome oxidase vesicles with high oxidase activity and respiratory control ratio (greater than 3.5) were characterized by the freeze-etch technique for electron microscopy. Through this technique, cytochrome oxidase were found to be present on inner membrane. By locating cross-fractured vesicles in the same preparation, cytochrome oxidase particles were seen to extend across the phospholipid bilayer membranes. When cytochrome oxidase was added to preformed liposomes, respiratory control was not observed al-

though high oxidase activity was maintained. In this preparation the cytochrome oxidase particles were located on the outer vesicle membrane surface. Such observations provided direct evidence that cytochrome oxidase is found in a transmembranous position in closed, active cytochrome oxidase vesicles that have respiratory control.

53. FUSION OF PHOSPHOLIPID VESICLES RECONSTITUTED WITH CYTOCHROME C OXIDASE AND MITOCHONDRIAL HYDROPHOBIC PROTEIN.

Miller C, Racker E
Department of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, New York 14853
J Membr Biol; 26(4):319-333 1976

Reconstituted cytochrome oxidase liposomes were fused with liposomes reconstituted with mitochondrial hydrophobic protein, which acts as a membrane-bound uncoupler of cytochrome oxidase. Fusion was assayed by the loss of respiratory control of cytochrome oxidase as measured by the increased rate of ascorbate oxidation induced by hydrophobic protein when both proteins shared the same vesicles. Fusion was dependent on the presence of phosphatidylserine in the liposomes and Ca++ in the aqueous medium. Phosphatidylcholine-phosphatidylserine liposomes required higher concentrations of phosphatidylserine and Ca++ than did phosphatidylethanolamine-phosphatidylserine liposomes. Cytochrome oxidase vesicles containing high concentrations of phosphatidylserine showed little or no respiratory control, while those with lower concentrations showed high respiratory control; respiratory control could be induced by fusing cytochrome oxidase vesicles containing high phosphatidylserine with protein-free liposomes containing low phosphatidylserine concentration. If cytochrome oxidase vesicles and hydrophobic protein vesicles were perfused separately for 15 min, they lost the ability to fuse upon being subsequently mixed together. (Author Abstract)

54. INCORPORATION OF BIOLOGICALLY ACTIVE PROTEINS INTO LIPOSOMES.

Eytan G, Matheson MJ, Racker E
Section Biochemistry, Cornell Univ., Ithaca, N.Y.
FEBS Lett; 57(2):121-125 1975

A procedure for incorporation of various mitochondrial proteins into preformed liposomes is outlined. Phospholipid suspensions containing various amounts of lysolecithin and phosphatidylethanolamine: phosphatidylcholine: cardiolipin (1: 1: 0.5) were sonicated to clarity and then incubated with cytochrome oxidase at 0 C. The optimal amount of lysolecithin required for enzyme incorporation was 10-20% of the total lipids. Most of the cytochrome oxidase appears to be oriented unidirectionally, and its incorporation did not require opening of vesicles since little ion leakage was detected in (86) Rb-labeled liposomes. Cytochrome oxidase incorporation also occurred in the presence of cholate (0.1 and 1%). Incorporation of complex III was observed with 10% lysolecithin and 1% cholate. Lysolecithin-containing liposomes incorporated hydrophobic protein and catalyzed a rapid (32) Pi-adenosine triphosphatase exchange. Reconstitution of this exchange by cholate occurred only at the higher concentration. Since lysolecithin is present in mitochondria and phospholipase A2 , which catalyzes the conversion of phosphatidylcholine into lysolecithin, is present in mitochondrial membranes, the procedure described may serve as model for incorporation of proteins into preexisting membranes.

55. EFFECT OF CYTOCHROME B 5 ON THE SIZE, DENSITY, AND PERMEABILITY OF PHOSPHATIDYLCHOLINE VESICLES.

Holloway PW, Katz JT
Department of Biochemistry, University of Virginia School of Medicine, Charlottesville, Virginia 22901
J Biol Chem; 250(23):9002-9007 1975

Cytochrome b 5, isolated from rabbit liver by a procedure using detergent, was incubated with phosphatidylcholine bilayer vesicles at 37 degrees for 30 min. A comparison of a number of physical properties was made between the cytochrome b5 phosphatidylcholine complex (at a molar ratio of 1:1000) and the phosphatidylcholine vesicles. The binding of the protein to the vesicle caused no aggregation and no detectable change in Stokes radius of the vesicle as monitored by gel filtration. Only small increases in s20 (from 2.67 up to 3.82 x 10(-13) s) and density (from 1.025 up to 1.042 g ml(-1)) were observed upon binding of the cytochrome b5 to phosphatidylcholine vesicles. At molar ratios of 5:1000, and above, two types of complexes could be detected by sucrose density gradient centrifugation: one had a molar ratio of approximately 4:1000 (density approximately 1.066 g ml(-1)) the other, a more constant ratio of 20:1000 (density greater than 1.107 g ml(-1)). Cytochrome b5 was also incubated with phosphatidylcholine vesicles prepared with ferricyanide trapped inside. The leakage of the ferricyanide from inside the vesicles was increased when cytochrome b5 was present, but the vesicles, although leaking, were not completely depleted of their ferricyanide, and so must still be intact. It is suggested that at molar ratios of cytochrome b5, to phosphatidylcholine below 5:1000, the binding of the protein causes minimal change in vesicle structure. (Author Abstract)

56. RECONSTITUTION OF PROLACTIN RECEPTORS IN ARTIFICIAL LIPID VESICLES (MEETING ABSTRACT).

Bhattacharya A, Vonderhaar BK
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20014
J Cell Biol; 79(2,part2):64a 1978

Reconstitution of membrane proteins into artificial phospholipid vesicles has been a useful system to study the interaction of phospholipids with membrane proteins. Most of the studies of this nature have involved incorporation of mitochondrial or microsomal membrane proteins. In this study we have been able to reconstitute mouse liver membrane proteins containing prolactin receptors into phospholipid vesicles using various exogenous phospholipids. Proteins from crude microsomal membranes were solubilized by 1% Triton X-100. Reconstitution was performed using both sonication and dialysis techniques. Similar results were obtained with both methods. Vesicles were purified by sedimentation through a cushion of 30% sucrose. Dipalmitoyl phosphatidyl choline containing vesicles showed max prolactin binding activity when a protein to lipid ratio of 1:5 was used during the reconstitution reaction. The resulting vesicles contained a protein to lipid ratio of approx 1:1 by wt. The affinity constant of the prolactin binding reaction was 1.6 x 10(9) M(-1) and the number of binding sites was found to be 144 femtomoles per mg protein. When the vesicles were formed below and above the phase transition temperature of the phospholipid used, no significant difference in the prolactin binding characteristic was observed. Integration of the receptor protein into the vesicles, as opposed to physical adsorption, is necessary for maximum activity of the receptor. Further properties of the receptors in the vesicles re-

constituted under a variety of conditions will be discussed. (no Refs)

57. BINDING OF DIPHTHERIA TOXIN TO PHOSPHOLIPIDS IN LIPOSOMES (MEETING ABSTRACT).
Iglewski BH, Alving CR, Urban KA, Moss J, Sadoff JC
Walter Reed Army Inst. Res., Washington, DC, 20012
Fed Proc; 38(3,part1):824 1979

Diphtheria toxin bound to the phosphate portion of some, but not all, phospholipids in liposomes. Of those tested, liposomes to which toxin did not bind consisted of dimyristoyl phosphatidylcholine (DMPC)/cholesterol (CHOL), and DMPC/CHOL plus 20 M% (compared to DMPC) of phosphatidylinositol. In the order of relative effectiveness, inclusion of 20 M% of the following lipids in the liposomes resulted in toxin binding: dipalmitoyl phosphatidic acid (calcium salt), dicetyl phosphate (DCP), phosphatidylinositol phosphate, cardiolipin, dipalmitoyl phosphatidic acid (sodium salt), and phosphatidylserine. Binding of toxin to liposomes consisting of phosphatidylcholine/ CHOL/DCP was inversely related to the fatty acyl chain length of phosphatidylcholine (lauroyl greater than myristoyl greater than palmitoyl greater than stearoyl). The least binding occurred with liposomes in which phosphatidylcholine was replaced by sphingomyelin. Binding of toxin was inhibited by uridine triphosphate, ATP, phosphocholine, p-nitro-phenylphosphate, and phosphate-buffered saline, but not by uracil or normal saline. We conclude that diphtheria toxin binds specifically to the phosphate portion of certain phospholipids, and that binding may be influenced by the composition of adjacent phospholipids that do not bind toxin. (no Refs)

58. LATERAL TRANSPORT OF AN AMPHIPATHIC APOLIPOPROTEIN BOUND TO PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLCHOLINE/CHOLESTEROL BILAYERS (MEETING ABSTRACT).
Vaz WL, Wu ES, Jacobson K
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Biophys J; 25(2,part2):178a 1979

Lateral diffusion of the amphipathic apolipoprotein, Apo C-III, labeled with fluorescein, has been studied using the method of fluorescence recovery after photobleaching in bilayers of dipalmitoyl phosphatidylcholine (DPPC), egg phosphatidylcholine (EPC), and a 1:1 molar ratio mixture of EPC and cholesterol (EPC/CHOL). In DPPC bilayers plots of the diffusion coefficient (D) vs temperature show different slopes below 30 C and above 35 C. Comparison of cholate-dialyzed DPPC liposomes prepared in the presence (lipid/protein molar ratio of 50) and absence of protein using 16-anthroyl palmitate as a fluorescence polarization probe of the lipid phase transition indicates that both preparations show a main transition at about 42 C but the protein containing preparation does not show the pre-transition at about 35 C. Also, the protein containing liposomes show a large turbidity change at about 35 C which is not seen in the absence of the protein. In DPPC bilayers D is about 2 x 10(-9) cm(2)/sec at 20 C and about 9 x 10(-8) cm(2)/sec at 45 C. Arrhenius activation energies for the diffusion process in DPPC bilayers are 28.5 and 7.0 kcal/mole between 15 and 30 C and between 35 and 45 C, respectively. No breaks in the slopes of plots of D vs temperature are seen in EPC and EPC/CHOL bilayers between 10 and 40 C. In EPC and EPC/CHOL bilayers at 20 C D is about 3 x 10(-8) cm(2)/sec and 1.4 x 10(-9) cm(2)/sec, respectively and the Arrhenius activation energies between 15 and 35 C are 8.1 and 15.1 kcal/mole, respectively. (no Refs)

59. INTERACTION OF MICROTUBULE PROTEINS WITH SIMPLE ARTIFICIAL MEMBRANES (MEETING ABSTRACT).
Caron JM, Berlin RD
Dept. Physiology, Univ. Connecticut Health Center, Farmington, CT, 06032
Fed Proc; 38(3,part1):797 1979

Microtubules (MT) have been implicated in the control of various surface phenomena. In additon, tubulin (the major protein subunit of MT) has been demonstrated in isolated membranes, but the molecular basis of the tubulin-membrane interaction and its function is unknown. We have studied the interaction of tubulin with unilamellar synthetic phospholipid vesicles of dimyristoyl phosphatidylcholine. Tubulin and associated high mol wt proteins are selectively adsorbed from soluble supernatants of brains or tubulin purified through one or two cycles of MT assembly and disassembly. The composition of adsorbed proteins is essentially equivalent to that achieved in parallel cycles of assembly and disassembly, and thus liposome adsorption and MT assembly may be governed by similar forces. Adsorption leads to highly ordered aggregation or fusion of liposomes into stacks or multilamellar structures. In additon, we show that adsorption is associated with the formation of intermolecular disulfide bonds. These bonds of the lipsome-protein structure are inaccessible to reducing agents in the external aqueous milieu, but are readily reduced following detergent extraction. The evidence is consistent with strong and specific tubulin interactions with simple bilayer membranes. (no Refs)

C.
Interactions of liposomes with other drugs and chemicals

60. CA2+-INDUCED FUSION OF PHOSPHOLIPID VESICLES MONITORED BY MIXING OF AQUEOUS CONTENTS.
Wilschut J, Papahadjopoulos D
Cancer Res. Inst., Univ. California, Sch. Medicine, San Francisco, CA, 94143
Nature; 281(5733):690-692 1979

The kinetics of phospholipid vesicle fusion were studied by means of an assay based on mixing of vesicle contents. One population of vesicles was allowed to encapsulate terbium (Tb3+) ions as TbCl3, and another population was allowed to encapsulate dipicolinic acid (DPA). In fusion of the vesicles the contents were mixed with the formation of the Tb(DPA)(3-) complex which produced a 10(4)-fold enhancement of the Tb fluorescence. Leakage or release of vesicle contents was not registered as fusion because Ca++ and EDTA, both present in the external medium, strongly interfered with formation of the fluorescent Tb(DPA)(3-) complex through their interaction with DPA and Tb+++, respectively. Fusion, monitored as vesicle content mixing, was induced by 1.5 milliM Ca++, and leakage monitored in a separate experiment by the release of carboxyfluorescein (CF) from similar vesicles. Although the release of vesicle contents, as determined by increasing CF fluorescence, started immediately after Ca++ addition, its rate was much lower than that of the Tb fluorescence increase. This indicates that fusion proceeded more rapidly than the release of vesicle contents. The eventual decrease of Tb fluorescence was consistent with the release and dissociation of the Tb(DPA)(3-) complex in the medium. Calcium, which slowly entered the vesicles, was able to bind to the

inner membrane, thus causing subsequent collapse of the fused vesicles and further release of contents. (18 Refs)

61. PHOSPHOLIPID VESICLE FUSION MONITORED BY FLUORESCENCE ENERGY TRANSFER.

Gibson GA, Loew LM
Dept. Chemistry, State Univ. New York at Binghamton, Binghamton, NY, 13901
Biochem Biophys Res Commun; 88(1):135-140 1979

Ca++ mediated fusion of phosphatidyl serine (PS) vesicles was observed on the basis of the Forster resonance energy transfer between 2 amphipathic probes. Such energy transfer was found to occur only in the presence of fusion of PS vesicles. A system is presently under construction which utilizes this technique to study the kinetics of PS vesicle fusion. (9 Refs)

62. THE INTERACTION OF PHOSPHOLIPID VESICLES WITH PLANAR PHOSPHOLIPID BILAYERS: THE EFFECT OF CALCIUM AND OTHER DIVALENT IONS (MEETING ABSTRACT).

Duzgunes N, Ohki S
Dept. Biophysical Sciences, State Univ. New York at Buffalo, Buffalo, NY, 14214
Biophys J; 25(2,part2):179a 1979

The interaction of unilamellar phosphatidylserine (PS)/phosphatidylcholine(PC) (1:1) vesicles with planar PS bilayers was followed by measuring the conductance of the latter. When the [Ca++] in the aqueous soln was raised to a threshold value of 3-5 milliM (mM) the conductance began to fluctuate and sharply increase, possibly because of the incorporation of domains of PC into the bilayer or due to individual fusion events. This concentration range was not sufficient to induce the aggregation of the vesicles, which preferentially interacted with the PS membrane. If vesicles were added to the soln already containing 5 mM Ca++ the conductance was unaffected, but specks developed on the planar membrane, most likely indicating adhesion of the vesicles. Further increasing the Ca++ initiated the fluctuations of conductance. Thus, the introduction of Ca++ and not merely its presence seemed to be essential for 'fusion'. Multilamellar vesicles did not affect the conductance appreciably when the [Ca++] was increased up to 10 mM. The threshold concentrations at which Ba++, Sr++ and Mg++ mediated the interaction of unilamellar vesicles with bilayers were, respectively, about 1 mM, 2 mM and 3 mM. The interaction of PS bilayers with PS vesicles containing gramicidin A as a probe was enhanced upon raising the [Ca++] from 0.9 to 1.2 mM, as detected by an abrupt increase in the ionophore-induced conductance, interpreted to be due to the close contact or fusion of the vesicles with the planar membrane. The effect of Ca++ could be correlated with fusion phenomena in vesicle-vesicle and vesicle-monolayer interactions. (no Refs)

63. DIVALENT CATION-INDUCED INTERACTION OF PHOSPHOLIPID VESICLES WITH MONOLAYER MEMBRANES (MEETING ABSTRACT).

Ohki S, Duzgunes N
Dept. Biophysical Sciences, SUNY at Buffalo, Buffalo, NY, 14214
Biophys J; 25(2,part2):179a 1979

The effects of phospholipid vesicles and divalent cations in the subphase soln on the surface tension (gamma) of phospholipid monolayer membranes were studied in order to elucidate the nature of the divalent cation-induced vesicle-membrane interaction. Various concentrations of unilamellar phospholipid [phosphatidylserine (PS), phosphatidylcholine (PC), and their mixtures] vesicles and divalent cations were introduced into the subphase soln of the monolayers. The changes in gamma of monolayers, with respect to divalent ion concentrations and time, were measured with a teflon Wilhelmy plate. When a PS monolayer and vesicles of PS:PC (1:1) were used, the critical, or threshold concentrations of divalent cations, which produced large reductions in gamma of the monolayer were: 16 milliM (mM) for Mg++, 7 mM for Sr++, 6 mM for Ca++, 3.5 mM for Ba++ and 1.8 mM for Mn++. With a PC monolayer and PC vesicles, up to 25 mM of any divalent ion used produced no change in gamma. For a PS monolayer and PC vesicles, the order of divalent ion concentrations needed to effect the large reduction in gamma was Mg++ greater than Ca++ greater than Mn++ and their critical concentrations were in between the former two cases. The threshold concentrations also depended upon vesicle concentrations as well as the area per molecule of monolayers. For PS monolayers and PS/PC (1:1) vesicles, above the critical concentrations of Mn++ and Ca++, gamma decreased to a value close to the equilibrium pressure of the monolayers within 0.5 hr. This decrease in gamma of the monolayers, which was not reversible upon the addition of EDTA, is interpreted partly as the consequence of fusion of the vesicles with the monolayer membranes. The order and magnitude of divalent cation concentrations at which PS/PC (1:1) and PS vesicle suspensions showed a large increase in turbidity were similar to those obtained in the above mentioned experiments. (no Refs)

64. DIVALENT CATION INTERACTIONS WITH PHOSPHATIDYLSERINE (PS) VESICLES: INHIBITION OF BOTH THE MARKED PREFERENCE OF PS FOR CA2+ OVER MG2+ IN COMPETITION EXPERIMENTS AND THE UNIQUE CA-INDUCED CHAIN CRYSTALLIZATION BY THE PROTEIN SPECTRIN (MEETING ABSTRACT).

Newton C
Kalamazoo Coll., Kalamazoo, MI, 49007
Biophys J; 25(2,part2):179a 1979

Binding studies of Ca2+ and Mg2+ to phosphatidylserine (PS) vesicles after equilibrium dialysis indicate that both cations are able to form stoichiometric (2:1) PS/metal complexes with the apparent binding constant for Ca2+ being about 2.5 x greater than for Mg2+. Binding studies of Ca2+ in the presence of Mg2+ indicate that Ca2+ is highly effective in competing with and displacing Mg2+ to a degree much more pronounced than that expected from the apparent binding constants of each ion alone. Differential scanning calorimetry reveals definite differences in the thermal properties of the PS/Ca and PS/Mg complexes. The large protein spectrin binds to PS vesicles in the presence of Ca2+ or Mg2+ without markedly effecting the binding of either divalent cation. However, the presence of spectrin drastically affects the competition between the two divalent metal ions so that it now approximates that expected from the apparent binding constants. Spectrin is also effective in short-term inhibition of the unique PS/Ca crystalline complex. Thus in the presence of spectrin, the effects of Ca2+ and Mg2+ are similar. One interpretation of these results is that the unique effects of Ca2+ involve close apposition of vesicle membranes with the strong possibility of an intermembrane trans-complex between Ca2+ and PS headgroups on both membranes. Binding of metal ions to PS headgroups on only one bilayer (cis-complex) would occur with Mg2+ alone or with Ca2+ when spectrin sterically hinders close vesicle-vesicle contact. The significance

of this proposal for mechanisms of membrane fusion will be discussed. (no Refs)

65. DIVALENT CATION ENHANCEMENT OF THE AGGLUTINABILITY BY SOYBEAN LECTIN OF LIPOSOMES PREPARED FROM TOTAL LIPID OF ERYTHROCYTES AND OF ERYTHROCYTE MEMBRANES.

Rendi R, Vatter AE, Gordon JA

Dept. Pathology, Univ. Colorado Medical Center, Denver, CO, 80262

Biochim Biophys Acta; 550(2):318-327 1979

CaCl2 or MgCl2 but not NaCl enhances the soybean lectin-induced agglutination of liposomes prepared from total lipids of RBC membranes. The addition of purified phosphatidylserine to the total lipids of RBC membranes before the formation of liposomes inhibits lectin-induced agglutinability of the preparation in the absence of CaCl2, but not in its presence. When preformed phosphatidylserine liposomes are added to liposomes of total lipids of RBC ghosts, they do not inhibit agglutination, indicating that phosphatidylserine does not inhibit the lectin directly. CaCl2 or MgCl2 but not NaCl also stimulates the soybean lectin-induced agglutination of human RBC membranes. Electron micrographs indicate that the liposome preparations are multilamellar and separate even in the presence of CaCl2. When such liposomes are treated with lectin with or without CaCl2, the electron micrographs show significant agglutination without apparent fusion. The reversal of the agglutination of liposomes by specific sugars followed by turbidimetric and electron microscopic techniques supports the conclusion that CaCl2 stimulated lectin-induced agglutination is unaccompanied by fusion. The stimulation by divalent cations of lectin-induced agglutination of RBC ghosts or of our liposomes may be due to a decrease in apparent surface charge of these membrane systems. (Author abstract) (17 Refs)

66. INTERACTION OF DNA AND LIPOSOMES AS A MODEL FOR MEMBRANE-MEDIATED DNA DAMAGE.

Pietronigro DD, Jones WB, Kalty K, Demopoulos HB

Dept. Pathology, New York Univ. Medical Center, New York, NY 10016

Nature (Lond); 267(5606):78-79 1977

The damaging consequences to the biological activity of bacterial-transforming DNA in oxidizing liposomal suspensions are reported. Incubation mixtures of liposomes and Bacillus subtilis or calf thymus DNA were prepared. The concentration of DNA had no effect on the induction period, which was approx 21 hr. Lipid oxidation was retarded by the DNA in a concentration-dependent manner. This suggests that DNA interacts with the oxidizing model membrane system as a free-radical acceptor or a trapping agent. Methyl arachidonate-enriched phosphatidylcholine (PCMA) liposomes demonstrated a higher rate of oxidation than phosphatidylcholine (PC) liposomes. At various times during the experiment, DNA was isolated from both the PCMA and PC liposomal suspensions and assayed for transforming activity. At 16 hr the PCMA liposomes decreased the DNA transforming activity by a factor of 2, but the PC liposomes caused no damage. By 36 hr, however, the PCMA liposomes decreased the activity by a factor of 3,000, and PC liposomes decreased by a factor of 8. After 68 hr both suspensions showed a decrease in activity by a factor of 3,000. DNA incubated with PC and PCMA liposomes in standard saline citrate did not undergo autooxidation. The results indicate that oxidation of highly organized lipid bilayers can damage DNA. (30 Refs)

67. INCORPORATION OF MACROMOLECULES WITHIN LARGE UNILAMELLAR VESICLES (LUV).

Papahadjopoulos D, Vail WJ

Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263

NY Acad Sci; 259-264 1978

68. CELL SURFACE CARBOHYDRATES FOR TARGETING STUDIES.

Ponpipom MM, Bugianesi RL, Shen TY

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Can J Chem; 58(3):214-220 1980

Syntheses of a series of glycolipids with 6-(5-cholesten-3beta-yloxy)-1-thiohexane as the aglycon and the following carbohydrates as surface determinants are described: D-glucose, D-mannose, D-galactose, 2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-galactose, L-fucose, L-arabinose, D-xylose, N-acetyl-D-neuraminic acid, lactose, and cellobiose. These 6-(5-cholesten-3beta-yloxy)hexyl 1-thioglycopyranosides have been incorporated into phospholipid vesicles for in vivo tissue distribution studies. (Author abstract) (41 Refs)

69. LACTOPEROXIDASE-CATALYZED IODINATION OF SURFACE MEMBRANE LIPIDS.

Mersel M, Benenson A, Doljanski F

Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel

Biochem Biophys Res Commun; 70(4):1166-1171 1976

Lactoperoxidase-catalyzed iodination of surface membrane lipids was studied in primary chick embryo cell cultures. During this iodination process, surface membrane lipids were also iodinated through an enzyme-dependent step. Phosphatidylcholine, cholesterol-phosphatidylcholine *liposomes* and confluent secondary cultures of chick embryo cells were iodinated by the lactoperoxidase-glucose oxidase-glucose I125 procedure. Liposomes were efficiently labeled. In the cells, 20-30% of the radioactivity was found in proteins and 20-30% in the lipids. Both neutral and polar lipids were found to bind [I125] covalently. Controls in which lactoperoxidase was omitted showed less than 6% of the radioactivity found in liposomes or cells labeled with the enzyme.

70. CHARACTERIZATION OF DRUG-MEMBRANE INTERACTIONS USING THE LIPOSOME SYSTEM.

Tritton TR, Murphree SA, Sartorelli AC

Dept. Pharamacology, Yale Univ. Sch. Medicine, New Haven, CT 06510

Biochem Pharmacol; 26(24):2319-2323 1977

Liposome vesicles may be used to provide structural and/or dynamic information on drug-membrane interactions. Drugs and chemical agents can affect membrane fluidity, permeability, spatial organization, fusion potential, charge distribution, and density. The interactions of anesthetics and liposomes have been studied using nuclear magnetic resonance, low field continuous wave protons, electron spin resonance, differential scanning calorimetry, and fluorescence polarization. The role of cholesterol in membrane interactions has also been studied using similar techniques. It has been shown that adriamycin can affect cell membranes as well as cellular DNA. The development of specific membrane-active drugs may be facilitated by using the simple liposome system. (37 Refs)

71. EVIDENCE FOR A LARGE INTERNAL PRESSURE IN BIOLOGICAL MEMBRANES.

Conrad MJ, Singer SJ
Dept. Biology, Univ. CA, San Diego, La Jolla, CA, 92093
Proc Natl Acad Sci USA; 76(10):5202-5206 1979

We have developed a method (hygroscopic desorption) for measuring the binding of small molecules to membranes. With this method, we have found that the binding of the amphipathic compounds chlorpromazine, 2,4-dinitrophenol, and 1-decanol to various cell membranes is remarkably low, with partition coefficients, Kp no larger than about 0.1. On the other hand, with *phospholipid vesicles* of large or small diameters, Kp values for these compounds were much larger. The results suggest that there exists in membranes a large internal pressure that excludes the amphipaths from the membranes and that does not exist in phospholipid vesicles. (Author abstract) (16 Refs)

72. THE INCORPORATION OF DDT AND RELATED COMPOUNDS INTO LECITHIN BILAYERS.

Reinert JC, Tinsley IJ
Environmental Health Sciences Center, Oregon State Univ., Corvallis, OR 97331
Pestic Biochem Physiol; 7(6):578-587 1977

The extent of incorporation of chlorophenothane (DDT) and several of its analogs into the hydrophobic interior of lecithin bilayers was monitored by nuclear magnetic resonance (NMR). Samples containing egg-yolk lecithin combined with DDT and three analogs were examined by NMR and electron microscopy. Results showed that bis-(p-chlorophenyl)- acetic acid (DDA) ring protons exhibited a well-resolved NMR spectrum, suggesting that the chemical is incorporated into the fluid interior of the lipid bilayers. The behavior in lecithin bilayers of methyl-bis-(p-chlorophenyl)-acetate (MDDA) was identical to that observed for DDA. When 2,2-bis-(p-chlorophenyl)-1,1-dichloroethylene (DDE) and lecithin were combined, NMR results showed that the chemical shift of the two distant ring protons of DDE was greater than the shift in DDA, indicating a resolved doublet. When DDT and lecithin were combined NMR results indicated that little DDT was incorporated into the lipid bilayers. Thus, the amount of the different compounds which can be taken up into the lipid in aqueous media varies, and this difference is not related to the organic:aqueous partition coefficients of the analogs. The amount of DDT which could be incorporated into the bilayers was much lower than the levels of other more water-soluble analogs. (25 Refs)

73. MECHANISM OF 2-NAPHTHYLAMINE OXIDATION CATALYZED BY PIG LIVER MICROSOMES.

Poulsen LL, Masters BS, Ziegler DM
Clayton Foundation Biochemical Inst., Dallas, TX
Xenobiotica ; 6(8):481-498 1976

At least three different microsomal components influence the rates of the 2-naphthylamine-dependent oxidation of NADPH and uptake of oxygen, catalyzed by pig liver microsomes. In these microsomes the 2-naphthylamine-dependent NADPH oxidation, oxygen reduction, and hydroxylamine formation were linear with time for 6 min. Between 6-8 min, there was a sharp increase in NADPH oxidation and oxygen uptake coinciding with an abrupt loss of hydroxylamine from the medium. The initial rate of N-oxidation correlated with the microsomal concentration of mixed-function amine oxidase, and the extent of linear accumulation of hydroxylamine was dependent on microsomal NADPH-cytochrome c reductase activity and concentration of lipid. Antisera to the NADPH-cytochrome c reductase decreased the linear reaction time from 7 min to less than 3 min but had no effect on the initial rate of 2-naphthylamine N-oxidation. The lipid present in the microsomes was also involved in stabilizing the hydroxylamine formed during the initial phase of the reaction. The microsomal catalyzed N-oxidation of 2-naphthylamine could be duplicated by a system composed of the isolated NADPH-cytochrome c reductase, the purified mixed-function amine oxidase, and a *nonspecific lipoprotein membrane or lipid phase* (synthetic lecithin liposomes). The contribution of each component to the oxidation of 2-naphthylamine in the reconstituted system was assessed by varying the concentration of each independently of the other two components. The initial rate of hydroxylamine formation was directly proportional to the concentration of the mixed-function amine oxidase, supporting the conclusion that the initial N-oxidation of 2-naphthylamine by pig liver microsomes is catalyzed by this oxidase. The liposomes decreased the hydroxylamine autooxidation rate and permitted more of this product to accumulate in the reaction medium. The reductase catalyzed the reduction of the oxidation product, 2-nitrosonaphthalene, back to the hydroxylamine and allowed retention of increasing amounts of hydroxylamine in the medium. (32 refs)

74. FREE RADICALS AND CARCINOGENESIS. SOME PROPERTIES OF THE NITROXYL FREE RADICALS PRODUCED BY COVALENT BINDING OF 2-NITROSOFLUORENE TO UNSATURATED LIPIDS OF MEMBRANES.

Floyd RA, Soong LM, Stuart MA, Reigh DL
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Arch Biochem Biophys; 185(2):450-457 1978

The reaction of 2-nitrosofluorene (NOF) with albino Sprague-Dawley rat liver microsomes was investigated. NOF reacted with 2,3-dimethyl-2-butene to produce a stable nitroxyl free radical (N-O-LAF) in a pseudo Diels-Alder reaction. NOF added to liposomes formed from rat liver microsomes to produce a free radical identical to that produced with microsomes. NOF formed the same amount of N-O-LAF at the same rate in heated microsomes as in unheated microsomes. This indicated that only the lipid fraction was involved in the reaction of NOF with the membranes. The amount of N-O-LAF formed increased hyperbolically in microsomes and liposomes as a function of NOF added. The amount of N-O-LAF formed reached a max, at which point the amount of free radical present was about 1% of both the amount of NOF added and the amount of phospholipid present. The half-maxima of N-O-LAF formation occurred at 50 uM NOF in *liposomes* but at 100 uM in microsomes. The electron spin resonance spectrum of N-O-LAF indicated that the nitroxyl free radical is rigidly fixed in the membrane. N-O-LAF was reduced by NADPH. There appeared to be a direct chemical reduction as well as an enzyme-mediated mechanism involving NADPH-potentiated electron flow in the microsomes. The reduced compound is reoxidized by ferricyanide added to microsomal membranes. (32 Refs)

75. TRANSPORT OF A CARCINOGEN, BENZO[A]PYRENE, FROM PARTICULATES TO LIPID BILAYERS.

Lakowicz JR, Bevan DR, Riemer SC
Dept. Biochemistry, Univ. Minnesota, P.O. Box 100, Navarre, MN, 55392

Biochim Biophys Acta; 629(2):243-258 1980

Fluorescence spectroscopic methods were used to investigate the effects of adsorption of benzo[a]pyrene to particulate matter on its rate of uptake into model membranes composed of dipalmitoyl L-alpha-phosphatidylcholine. From these experiments we conclude the following: (1) Adsorption of benzo[a]pyrene to four types of asbestos (anthophyllite, crocidolite, chrysotile, and amosite) and a variety of non-fibrous particles (hematite, silica, titanium, dioxide, porous glass and talc) results in increased rates of membrane uptake when compared with aqueous suspensions of benzo[a]pyrene microcrystals. Benzo[a]pyrene was not released from carbon black. (2) Asbestos-adsorbed benzo[a]pyrene was transferred to the membranes most rapidly. (3) Adsorption of benzo[a]pyrene to the surface of the particles is necessary for its enhanced transport into membranes. That is, simple mixtures of benzo[a]pyrene microcrystals and particulates do not show enhanced transport. (4) Particle-enhanced transport of benzo[a]pyrene is not correlated with the effects of the particles on vesicle integrity, binding of vesicles to the particles, or the concentrations of either particles or vesicles. The rate limiting step for transport of benzo[a]pyrene into vesicles appears to be its rate of desorption from the surface of the particle. Following desorption, membrane uptake of benzo[a]pyrene is rapid. (Author abstract) (no Refs)

76. PARTICULATE ENHANCED MEMBRANE UPTAKE OF 1,2-BENZANTHRACENE OBSERVED BY FLUORESCENCE SPECTROSCOPY.

Lakowicz JR, Englund F, Hidmark A
Freshwater Biological Inst., Dept. Biochemistry, Univ. Minnesota, P. O. Box 100, Navarre, MN, 55392

Biochim Biophys Acta; 543(2):202-216 1978

The transfer of 1,2-benzanthracene (BA) from the silica-adsorbed state to *phospholipid vesicles* of dipalmitoyl-L-alpha-phosphatidylcholine was studied and compared with the rates of transfer from crystalline and microcrystalline aqueous dispersions. The fluorescence spectral shifts that occurred upon transfer of BA from the silica surface to the phospholipid vesicles were used to quantitate the membrane uptake of BA from particulates. The rate of BA uptake by the dipalmitoyl-L-alpha-phosphatidylcholine vesicles was independent of the lipid concentration, suggesting that the solubilization rate of BA in the aqueous phase was rate limiting. The rate of membrane uptake was also independent of the surface density of BA on silica, indicating that the BA molecules were uniformiy dispersed on the silica surface. Adsorption of BA to silica greatly enhanced its rate of transport into the vesicles, the silica-adsorbed BA being more rapidly transported into the vesicles than was microcrystalline BA at temperatures from 8 C to 42 C. Silica apparently did not disrupt the vesicles under the conditions used. The data indicate that particulates can act as cocarcinogens by enhancing the cellular uptake of carcinogens and by facilitating the expression of preneoplastic transformation. (27 Refs)

77. PARTICLE-ENHANCED MEMBRANE UPTAKE OF A POLYNUCLEAR AROMATIC HYDROCARBON: A POSSIBLE ROLE IN COCARCINOGENESIS.

Lakowicz JR, Englund F, Hidmark A
Freshwater Biological Inst., Univ. Minnesota, P.O. Box 100, Navatte, MN, 55392

JNCI; 61(4):1155-1159 1978

The effect of a particulate, silica, on the rate of membrane uptake of benz(a)anthracene (BA) was studied. The fluorescence emission spectrum and quantum yield of BA, when adsorbed to silica, underwent spectral shifts upon addition of *phospholipid vesicles*. These spectral changes appeared to result from the transfer of BA from the silica surface into the lipid bilayer. These spectral changes were used to measure the rates of membrane uptake of BA from the silica-adsorbed state and from the crystalline and microcrystalline states of BA. Adsorption of BA to silica resulted in an increased rate of uptake of BA into dipalmitoyl-L-alpha-phosphatidylcholine vesicles compared with the uptake rate into these vesicles from crystalline states. This particle-enhanced membrane uptake of chemical carcinogens may be of importance in explaining the enhanced carcinogenicity of polynuclear aromatic hydrocarbons in the presence of particulate matter. (28 Refs)

78. PARTICLE-MEDIATED MEMBRANE UPTAKE OF CHEMICAL CARCINOGENS STUDIED BY FLUORESCENCE SPECTROSCOPY.

Lakowicz JR, McNamara M, Steenson L
Freshwater Biological Inst., Univ. Minnesota, Navarre, MN, 55392

Science; 199(4326):305-307 1978

Because particulates and polynuclear aromatic hydrocarbons act as cocarcinogens, the uptake rate of chrysene N-ethylcarbazole, and 1,6-diphenylhexatriene from particulates and into *phospholipid vesicles* was studied by fluorescent emissions. Chrysene entered phospholipid bilayers much more rapidly from the silica-absorbed state than from a microcrystalline state. The fluorescence emissions of N-ethylcarbazole and 1,6-diphenylhexatriene also underwent large spectral shifts and/or changes in quantum yield upon uptake of the compounds from particulates by phospholipid vesicles. 1,6-Diphenylhexatriene was nonfluorescent on glass beads but highly fluorescent after transport into lipid vesicles. These findings indicate the feasibility of using fluorescence spectroscopy to measure the rates of exchange of polynuclear aromatic hydrocarbons from particulate matter to cell membranes. (14 Refs)

79. INTERACTIONS OF PHYSICAL MODEL OF THE MEMBRANE/CYTOPLASM INTERFACE WITH CO-CARCINOGENS.

Horton AW, Butts CK, Schuff AR
Univ. Oregon Health Sciences Center, Eugene, OR 97403

Colloid and Interace Science, Kerker M, ed. New York, Academic Press, Inc., Vol. V, 506 pp., 1976.

A buffered potassium chloride aqueous solution interfaced with a solution of selected membrane lipids was used as a physical model in the study of the interactions of cocarcinogenic hydrocarbons, alcohols, and esters with biological membranes. The rate of transfe. of sodium p-(p-anilinophenylazo)-benzene sulfonate (Orange IV), an anionic dye, from the aqueous phase to the organic lipid micelle phase under conditions of emulsification, was studied. Using phosphatidyl cholines as the primary lipid components, the kinetics of the transfer were found to be dependent on the fluidity of the micelles. A comparatively high rate of transfer of the dye was observed when egg phosphatidyl choline (2 double

bonds per molecule) was used. Equilibrium was reached in approx 10 min at 21 C with 70% of the Orange IV dye in the lipid phase. When lysolecithins were included in the organic phase, the kinetics of the transfer were markedly reduced. The combination of cholesterol with either phosphatidyl choline or lysolecithin in the organic phase produced a micelle which was found to be of intermediate fluidity and selectively and quantitatively sensitive to the n-alkanes that were found to increase the incidence of carcinogenesis. (15 Refs)

IV. INTERACTIONS OF LIPOSOMES WITH CULTURED CELLS AND TUMORS

A.

Cellular adhesion and uptake of liposomes in cell cultures

80. LIPOSOME-CELL INTERACTIONS. A RAPID ASSAY FOR CELLS IN SUSPENSION CULTURE.

Fountain MW, Chiovetti R, Kercret H, Parrish DO, Segrest JP
Dept. Veterinary Physiology and Pharmacology, Auburn Univ., Auburn, AL, 36830
Biochim Biophys Acta; 596(3):420-425 1980

A method has been developed for the rapid separation of cells in suspension from non-cell associated lipid vesicles in various assays for vesicle-cell interaction. Separation is achieved on a discontinuous Ficoll-Paque gradient. Cells and free vesicles are totally separated, as evidenced by both radiolabeled vesicles, and vesicles containing the fluorescent dye 6-carboxyfluorescein. The main advantages of this method are the rapidity, efficacy, and gentleness of the separation. Viability of the cells remains consistently high (greater than 96%) throughout the separation. Since this method involves a one-step centrifugation, it precludes the necessity for repeated washings of cells which have been incubated with lipid vesicles. (Author abstract) (19 Refs)

81. FLOW MICROFLUOROMETRIC MONITORING OF THE INTERACTION OF LIPID VESICLES WITH CELLS.

Hock D, Stohr M
Deutsches Krebsforschungszentrum Heidelberg, Institut fur Experimentelle Pathologie Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany, Federal Republic
Histochemistry; 52(2):97-103 1977

The application of flow microfluorometric techniques to the study of liposome-cell interactions is presented. Liposomes with the fluorescent probe perylene inserted into their multilamellar layer were detected using a highly sensitive laser flow system. This system permitted the measurement of the weak fluorescence emitted by individual liposomes. The total fluorescence of cells that have incorporated liposomes could be measured and separated from that of unbound liposomes. Since the fluorescence of all the liposomes bound by a cell is additive, the total cellular fluorescence is a measure of the number of liposomes bound by the cells. The frequency distribution of liposomes and cells showed clear differences concerning both their size and fluorescence. Time-course analysis of cellular fluorescence spectra showed significant differences in the incorporation rates of cationic and anionic liposomes. The advantages of rapid data analysis by flow fluorescence methods is discussed in comparison with conventional radio-isotopic techniques. (19 Refs)

82. INFLUENCE OF INCORPORATED CEREBROSIDES ON THE INTERACTION OF LIPOSOMES WITH HELA CELLS.

Bussian RW, Wriston JC
Dept. Chemistry, Univ. Delaware, Newark, DE 19711
Biochim Biophys Acta; 471(2):336-340 1977

The composition of cell membranes may be changed by the incorporation of liposomes. The effect of synthetic cerebrosides on the fusion of neutral liposomes with HeLa cells in culture was studied. The incorporation of galactose-terminal cerebrosides into liposomes brought about the preferential incorporation of cholesterol into HeLa cells. Lactocerebroside had approx twice the effect on incorporation as galactocerebroside suggesting that the glucosyl moiety of the disaccharide allowed better interaction of the terminal galactose with the putative cell-surface receptor. The increased uptake is probably not from a change in the physical characteristics of the liposome membrane. The phenomenon appeared to be carbohydrate specific. It was estimated that the fusion was enhanced 7-fold by the presence of the lactocerebroside. It was concluded that this system would be well-suited for evaluating the distribution and character of galactose receptors with respect to membrane function. The system is less complex than in vivo systems and is free of potential complications due to glycoprotein recognition factors other than galactose. (14 Refs)

83. INFLUENCE OF INCORPORATED CEREBROSIDE ON THE UPTAKE OF LIPOSOMES BY HELA CELLS. (MEETING ABSTRACT).

Bussian RW, Wriston JC
Dept of Chemistry, Univ of Delaware, Newark, DE 19711
Fed Proc; 36(3):642 1977

While studying variables influencing rate and mechanism of uptake of liposomes, we have found that incorporation of certain cerebrosides stimulates uptake of neutral liposomes by HeLa cells 5- to 10-fold. Liposomes were made from phosphatidylcholine (PC), cholesterol and cerebroside in the mole ratio 7/2/1, respectively. Trace amounts of 14C-cholesterol were used to follow uptake. Liposomes were incubated with HeLa cells in Holmes' A3 medium supplemented with heat inactivated fetal calf serum, penicillin and streptomycin for 3 hrs at 37 degrees under 5% CO2. Liposomes prepared with lactocerebroside were taken up 5 to 10 times as well as those containing no cerebroside, or those containing glucocerebroside. A more modest stimulation of uptake was seen with liposomes containing galactocerebroside. Uptake in this system is chiefly by fusion in all cases, since addition of cytochalasin B had little or no effect. Increased uptake is not due to a change in liposome membrane fluidity, since uptake with liposomes containing N-palmitoyl dihydrosphingosine is the same as with liposomes made from PC and cholesterol alone. (Author Abstract)

84. SURFACE CAPPING OF LIPOSOMAL VESICLES (MEETING ABSTRACT).

Bourguignon LY, Rader RL
Dept. Biology, Wayne State Univ., Detroit, MI, 48202
J Cell Biol; 79(2,part2):51a 1978

Unilamellar phospholipid vesicles have been found to adsorb to the surfaces of both murine lymphocytes and human fibroblasts. Fluorescent vesicles composed of dipalmitoyl phosphatidylcholine (DPPC) and containing entrapped 6-carboxyfluorescein were used to examine the lipo-

some-cell interactions. After the cells were incubated for 1 hr at 4 C followed by warming to room temperature, the liposomes are aggregated into caps. However, prior fixation with 2% paraformaldehyde leads to binding of the liposomes over the entire cell surface. In the case of prefixed lymphocytes, the fluorescence occurs as a uniform ring around the periphery of the cells whereas the fibroblast surfaces are covered with random patches. The liposome capping phenomenon shares several common properties with conventional antibody- or lectin-induced surface capping. For example, both liposomally-induced and conventional capping are temperature and energy dependent, colchicine insensitive and cytochalasin B sensitive. In addition, binding of the liposomes is greatly reduced when the cells are trypsinized either before or after incubation with the liposomes. Our results suggest that liposomal capping involves binding of the vesicles to surface membrane proteins which are in turn either directly or indirectly associated with intracellular microfilaments. (no Refs)

85. PLASMA MEMBRANE-MEDIATED LEAKAGE OF LIPOSOMES INDUCED BY MURINE THYMOCYTES (MEETING ABSTRACT).

Kercret H, Chiovetti R, Segrest JP
Dept. Pathology, Univ. Alabama Medical Center, Birmingham, AL
J Cell Biol; 83(2,part2):76a 1979

The interactions between artificial phospholipid vesicles (liposomes) and BW 5147 murine thymocytes in suspension culture have been investigated. Vesicles were prepared by either incorporating fluorescent lipid (N-4-nitrobenzo-2-oxa-1,3-diazole phosphatidylethanolamine) or by entrapping the fluorescent dye 6-carboxyfluorescein (6-CF) in vesicles in a self-quenched state (200 milliM). In some experiments, cells were separated from vesicles by a rapid (60 sec) centrifugation at 300 x gravity on discontinous Ficoll-Paque gradients. The association of liposomes with cells is linear during the first 30 min and plateaus between 30-90 min, indicating saturation kinetics. The increase in fluorescence of the cells is paralleled by an increased fluorescence in the liposome fractions, indicating that essentially all uptake can be accounted for by leakage and passive incorporation; less than 1% of uptake can be assigned to 'fusion'. The rates of leakage are similar for vesicles composed of pure phosphatidylcholine (PC) and 9:1 (wt/wt) PC:phosphatidylserine (PS), but PC:PS 8:2 vesicles demonstrate less than 10% of the leakage of PC vesicles. Leakage is dependent upon the concentration of cells, but is not the result of any metabolic byproducts or secreted substances. In addition, the induced leakage is dependent upon pH (max at pH 6.5) and temperature (max at 50 C), and when fit to Michaelis-Menten kinetics yields a decreasing Km in the presence of increasing amounts of 'inhibitor' (ie, non-6-CF containing) liposomes, suggesting competitive inhibition. Leakage is inhibited by incubation at 0 C and by boiling the cells for 20 min, and greater than 90% of the leakage is induced by a crude membrane pellet from hypotonically lysed cells. These studies implicate a membrane factor on BW thymocytes which is responsible for inducing liposomal leakage. The mechanism requires an initial adsorption of liposomes which is dependent upon electrostatic interactions. (no Refs)

86. INTERACTION OF LIPOSOMES WITH CULTURED CELLS: EFFECT OF SERUM.

Mayhew E, Gotfredsen C, Schneider YJ, Trouet A
International Inst. Cellular Molecular Pathology, Brussels, Belgium
Biochem Pharmacol; 29(6):877-886 1980

The binding of sonicated liposomes (small, mainly unilamellar) by cultured rat fibroblasts and mouse L1210 cells, in the presence or absence of serum, determined as micromoles phospholipid/mg cell protein, depends on the composition of the liposomes. Negatively charged solid liposomes (phospholipids below their phase transition temperature) were bound by cells several times more than fluid liposomes were under the same conditions. There was less binding, for each type of liposome studied in the presence of serum. Time, liposome concentration and temperature effects suggest that liposomes interact with the cultured cells studied by a two-stage process: an initial rapid step, probably adsorptive, followed by a second slower step. Cell fractionation studies showed that solid and fluid liposome phospholipids were treated similarly by the cells and equilibrated mainly at densities similar to those of plasma membrane marker enzymes. Further, after incubations with inulin entrapped in liposomes, there was no accumulation of [3H]inulin in lysosomal fractions. Whereas the data indicated that the liposomes studied were not endocytosed intact, there was also no evidence that 'fluid' liposomes rapidly fused with cells with their contents found in soluble fractions. Studies on liposomal permeability indicated, as has been suggested previously, that cholesterol is a key component for reducing the leakiness of liposomes in the presence of significant concentrations of serum. For short-term studies liposomes lacking cholesterol can be used for studies on cell binding or uptake of entrapped species, in the presence of serum, but in longer term studies the effects of serum make interpretation of data difficult in that type of liposome. (Author abstract) (34 Refs)

87. EFFECT OF FETAL CALF SERUM AND SERUM PROTEIN FRACTIONS ON THE UPTAKE OF LIPOSOMAL PHOSPHATIDYLCHOLINE BY RAT HEPATOCYTES IN PRIMARY MONOLAYER CULTURE.

Hoekstra D, Scherphof G
Laboratory of Physiological Chemistry, University of Groningen, Bloemsingel 10, 9712 KZ Groningen, The Netherlands
Biochim Biophys Acta; 551:109-121 1979

88. DISTRIBUTION OF NEGATIVELY CHARGED LIPOSOMES ON RAT LIVER HEPATOCYTES AND NON-HEPATOCYTES IN CELL SUSPENSION.

Freise J, Muller WH, Rauch S
Div. Gastroenterology Hepatology, Medizinische Hochschule Hannover, D-3000 Hannover 61, W. Germany
Exp Cell Res; 126(1):57-62 1980

The attachment of negatively charged multilamellar liposomes to rat liver parenchymal cells (PCs) and nonparenchymal cells (NPCs) was studied in vitro. The liposomes were labeled with (14C)-cholesterol, and they contained (3H)-labeled methotrexate. The behavior of the PCs in vitro was similar to that in vivo, but the rate of liposome attachment by the NPCs was 20-50 x lower than that observed in vivo. Dinitrophenol and iodoacetic acid reduced liposome uptake by 20%-30%. (13 Refs)

89. CATIONIC LIPOSOME INTERACTION WITH NORMAL AND TRANSFORMED RAT LIVER EPITHELIAL CELLS IN CULTURE. (MEETING ABSTRACT).

Tokes ZA, Der CJ, Todd JA
Cell Membrane Lab, LAC/USC Cancer Center; Dept. Biochemistry, USC School of Medicine, Los Angeles, Ca. 90033
Proc Am Assoc Cancer Res; 18:247 1977

At least two mechanisms are revealed in the uptake of cationic liposomes by normal and transformed liver epithelial cells in vitro. The earliest interaction is passive adsorption. The major mechanism of uptake, accounting for approxi-

mately 75-90%, is energy-dependent. The uptake of liposomes by transformed hepatocytes is greater than that observed with normal cells in suspension or with cultured monolayers. Lipid-sheet formation at the surface of cells is observed with electron microscopy. Internalization occurs rapidly; after 90 min, only 20% of the adsorbed liposomes are released by trypsin treatment. Ten- to 20-fold enhancement of methotrexate (MTX) uptake is observed when 3H-MTX is entrapped within the aqueous compartment. The presence of unloaded liposomes does not enhance the uptake of free 3H-MTX, indicating that the increase is due to entrapment rather than to an indirect stimulatory effect of liposomes on cellular transport. Attachment of cell membrane glycoproteins from organs other than liver to the cationic liposomes decreases uptake by hepatocytes. Normal lung-derived glycoproteins included in liposome membranes decreased the uptake of entrapped 3H-MTX by normal and transformed liver cells, but the uptake increased for the lung epithelial cells. (Author Abstract)

90. IN VITRO INTERACTION OF ZAJDELA ASCITES HEPATOMA CELLS WITH LIPID VESICLES.

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Lab. Physiological Chemistry, State Univ. Groningen, Medical Sch., Bloemsingel 10, 9712 KZ Groningen, Netherlands
Biochim Biophys Acta; 558(1):22-40 1979

We studied the in vitro interaction between Zajdela ascites hepatoma cells and small unilamellar vesicles, consisting of 14C-labeled phosphatidylcholine, cholesterol, and phosphatidylserine (M ratio 5: 4: 1), containing high intravesicular concentrations of carboxyfluorescein or fluorescein isothiocyanate tagged dextran. The entrapped markers were found to be associated with the cells to a lesser degree than the vesicle membrane marker. This discrepancy, which is slightly less pronounced for fluorescein isothiocyanate tagged dextran than for carboxyfluorescein, increases with incubation time and decreases with increasing vesicle lipid concentration in the incubation mixture. Vesicle-plasma membrane exchange of the vesicle lipid marker could not entirely explain the observed discrepancy. It is tentatively concluded that the gap mainly arises from a selective loss of entrapped dyes from vesicles actually interacting with the cell surface. Both spectrofluorimetric and fluorescence microscopic observations, as well as the relative insensitivity of vesicle uptake towards the presence of metabolic inhibitors, exclude a major contribution of endocytosis as a vesicle uptake route. We therefore conclude that vesicles are primarily internalized by a vesicle-cell fusion-like process. The observed discrepancy in uptake between entrapped materials and vesicle lipid is discussed in terms of a two-site vesicle-cell surface interaction model. (Author abstract) (23 Refs)

91. BIOCHEMICAL, MORPHOLOGICAL, AND ULTRASTRUCTURAL STUDIES ON THE UPTAKE OF LIPOSOMES BY MURINE MACROPHAGES.

Raz A, Bucana C, Fogler WE, Poste G, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(2):487-494 1981

The interaction of multilamellar liposomes with mouse peritoneal macrophages cultured in vitro has been examined. The principal mechanism of liposome uptake by these cells is by phagocytic engulfment. Studies with radiolabeled liposomes demonstrated that they are incorporated into macrophages as intact structures and that treatment of macrophages with inhibitors of phagocytosis prevents liposome uptake. Incubation of macrophages with liposomes containing encapsulated fluorescein-labeled bovine serum albumin resulted in localization of fluorescence within discrete cytoplasmic vacuoles. Ultrastructural observations confirmed that liposomes were internalized and were enclosed within phagosomes. Electron microscopy also revealed that, by 24 hr following phagocytosis, adjacent phagosomes containing liposomes prepared from bovine brain phosphatidylserine, egg phosphatidylcholine, and lysolecithin (mol ratio, 4.95/4.95/0.1) fused within the cytoplasm. In contrast, phagosomes containing neutral liposomes consisting solely of egg phosphatidylcholine did not fuse and remained as discrete single structures. Negatively charged bovine brain phosphatidylserine/egg phosphatidylcholine/lysolecithin liposomes were phagocytosed at a much faster rate (12x faster) than were neutral egg phosphatidylcholine liposomes. (Author abstract) (32 Refs)

92. LIPID VESICLES AS CARRIERS FOR INTRODUCING MATERIALS INTO CULTURED CELLS: INFLUENCE OF VESICLE LIPID COMPOSITION ON MECHANISM(S) OF VESICLE INCORPORATION INTO CELLS.

Poste G, Papahadjopoulos D
Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263
Proc Natl Acad Sci USA; 73(5):1603-1607 1976

The mechanisms involved in the uptake of uni- and multilamellar lipid vesicles by BALB/c mouse 3T3 cells have been investigated. Vesicles are incorporated into cells both by endocytosis and by a nonendocytotic mechanism which we propose involves fusion of vesicles with the plasma membrane. The nonendocytotic pathway predominates in the uptake of negatively charged vesicles composed of phospholipids that are 'fluid' (phosphatidylserine/phosphatidylcholine) at 37 degrees. Neutral 'fluid' vesicles (phosphatidylcholine) and negatively charged vesicles prepared from 'solid' phospholipids (phosphatidylserine/distearylphosphatidylcholine/dipalmitoylphosphatidylcholine) are instead incorporated largely by endocytosis. Uptake of the latter classes of vesicle is reduced (80-90% inhibition) by inhibitors of cellular energy metabolism and by cytochalasin B. Uptake of negatively charged fluid vesicles is reduced by only 30-40% after similar treatments. Prefixation of cells with glutaraldehyde inhibits endocytosis and uptake of neutral and negatively charged solid vesicles, but does not inhibit uptake of fluid charged vesicles. Prefixation of cells with osmium tetroxide prevents uptake of all classes of vesicles. Similar results are obtained with both uni- and multi-lamellar vesicles of the same composition, indicating that vesicle composition rather than size is more important in determining the pathway of uptake into cells. The different pathways involved in vesicle uptake are discussed in relation to the development of possible methods for targeting vesicles to specific intracellular sites. (Author Abstract)

93. IN VITRO INTERACTION OF L1210 CELLS WITH PHOSPHOLIPID VESICLES.

Jansons VK, Weis P, Chen T, Redwood WR
Dept. Microbiology, Coll. Medicine and Dentistry of New Jersey, New Jersey Medical Sch., Newark, NJ, 07103
Cancer Res; 38(3):47-51 1978

The effect of chemical composition on the uptake of liposomes by mouse leukemia L1210 cells was tested. Unilamellar liposomes were generated from phosphatidylcholine (PC), PC and cholesterol (Chol) (neutral), PC, Chol and phosphatidylserine (negatively charged), or PC, Chol and octadecylamine (positively charged). H3-inulin was added

to the liposomes as an internal radioactive marker. The uptake of the positively charged liposomes was markedly greater. Cells from younger cultures took up more liposomes than cells from older, stationary cultures. This difference was 2-fold with positively charged liposomes, and somewhat less with neutral ones. Uptake of positive and neutral liposomes was decreased at 2 C compared to 37 C. Cells incubated with positive liposomes showed a time-dependent increase in cell-associated radioactivity at 2 C; neutral liposomes did not give this effect. Addition of 5 millimolar sodium azide decreased uptake of neutral and positive liposomes. Addition of 20 millimolar 2-deoxyglucose (with sodium azide) decreased uptake even further. Uptake of positive liposomes increased slowly with time. Treatment with trypsin removed 40% of the radioactivity and treatment with neuraminidase or 0.6 N NaCl removed 50%. Reasons for differences in uptake of differently charged liposomes are discussed. (20 Refs)

94. INTERACTION OF PHOSPHOLIPID VESICLES WITH L1210 CELLS IN VITRO. (MEETING ABSTRACT).

Jansons VK, Chen T, Redwood WR
CMDNJ NJ Medical Sch, Newark, N. J. 07103
Proc Am Assoc Cancer Res; 18:249 1977

The in vitro uptake of phospholipid vesicles by murine L1210 cells was examined. Liposomes were generated by prolonged ultrasonication of aqueous dispersions of mixed lipids in the presence of radiolabeled inulin. Multilamellar vesicles were separated from unilamellar vesicles by column chromatography. Vesicle populations were examined by electron microscopy. Neutral vesicles were generated from egg yolk phosphatidylcholine and cholesterol, and surface charge was introduced via either phosphatidylserine or octadecylamine. Uptake was temperature-dependent and was decreased by metabolic inhibitors. Multilamellar and unilamellar liposomes were taken up to similar extents by these cells. However, positively charged vesicles were taken up to a greater extent than either neutral or negatively charged vesicles. The increase was only partially reversed by neuraminidase treatment. Cells in logarithmic growth phase took up more vesicles than cells in stationary phase. These studies suggest that the factors which influence the uptake of vesicles by neoplastic cells may vary depending on culture conditions and the cell line studied. (Author Abstract)

95. ADHESION OF PHOSPHOLIPID VESICLES TO CHINESE HAMSTER FIBROBLASTS.

Pagano RE, Takeichi M
Dept. Embryology, Carnegie Inst. Washington, Baltimore, MD 21210
J Cell Biol; 74(2):531-546 1977

In order to study membrane-membrane interactions, the adhesion of artifically generated *lipid membrane vesicles* to Chinese hamster V9 fibroblasts in suspension is used as a model system. Discussion of results includes analysis of evidence for vesicle-cell adsorption and possible modes of vesicle-to-cell adhesion. (41 Refs)

96. INFILTRATION OF MULTICELLULAR SPHEROIDS BY LIPID VESICLES (MEETING ABSTRACT).

Sridhar R, Barratt DG, Grant CW
Oklahoma Medical Res. Foundation, Oklahoma City, OK, 73104
Fed Proc; 38(3,part1):370 1979

Spheroids of V79 Chinese hamster lung cells are balls of tightly adhering cells which provide a good in vitro model of poorly vascularized solid tumors. All cells within spheroids are readily accessible to interaction with exogenously added lipid vesicles. Sonicated lipid vesicles (25 nanometer diameter; 5:9:1 wt ratio of cholesterol:egg phosphatidylcholine:phosphatidylserine) readily penetrated spheroids of up to 600 um diameter as judged by autoradiograms of serial histological sections through spheroids which had been exposed to lipid vesicles labeled with 14C-phosphatidylcholine or 3H-cholesterol in serum-free medium. About 90% of the radio-labeled cholesterol is extractable from the serial sections using a 2:1 chloroform:methanol mixture, and identifiable by thin layer chromatography. The density of radioactive decays is similar at all depths in the spheroid even for a half hr treatment time; and the amount of new lipid which can be associated with spheroid cells is directly proportional to the exposure time for up to 18 hrs. Lipid vesicles may provide a way of direct transmission of new membrane material (including water insoluble drugs) into solid tumors. (no Refs)

B.

Effects of liposomes and liposome components on growth, differentiation and metabolism in cultured cells and tumors

97. THE INTERACTION OF LIPOSOMES WITH CELLS: THE RELATION OF CELL SPECIFIC TOXICITY TO LIPID COMPOSITION.

Layton D, Luckenbach GA, Andreesen R, Munder PG
ICP, Avenue Hippocrate, 75, B-1200 Bruxelles, Belgium
Eur J Cancer; 16(12):1529-1538 1980

Liposomes, which have been proposed as agent carriers, can themselves produce a wide variety of effects on the viability of co-incubated cells. In this study we show that the lipid composition of empty liposomes produced varied effects on the viability, as measured by [3H]-thymidine incorporation, of leukemic cells and fibroblasts. Certain liposomal compositions, particularly those involving stearylamine, were highly toxic to both cell types. It is evident from this investigation that caution must be exercised in the choice of lipid composition if the effect of the liposomes is not to conceal that of the drug, or carried agent, either on the target cells in terms of therapeutic effect, or on normal cells in terms of toxicity. Normal lysophosphatides, having on acyl bond in sn-1, can be metabolized by both normal and leukemic cells; however the replacement of the acyl by an alkyl bond in a lysophosphatide requires an O-alkyl cleavage enzyme to be metabolized. Such an enzyme is present in a multifunctional oxygenase in normal cells but appears to be absent or inoperative in certain tumor cells. Coincubation of alkyl lysophosphatide containing liposomes is shown to produce selective destruction of L1210 leukemic cells; in addition the liposomal form of such analogs is suggested as being more effective against leukemic cells and less toxic to normal cells than when used in the free form. (Author abstract) (33 Refs)

98. ALTERATION OF MAMMALIAN CELLS BY INTERACTION WITH ARTIFICIAL LIPID VESICLES.

Dunnick JK, Rooke JD, Aragon S, Kriss JP
Department of Radiology, Stanford University Medical Center, Stanford, California 94305
Cancer Res; 36(7):2385-2389 1976

Artificial lipid vesicles interact with a variety of mammalian cells, including blood cells, spleen cells, and tumor cells, and during this interaction components can be transferred from the vesicle to the cell and from the cell to the vesicle. Transfer of intravesicular material is observed when artifical lipid vesicles carrying an intravesicular marker, 99mTc (as

TcO4 ion), are incubated with mammalian cells. When vesicles prepared with (14C) phospholipid are incubated with mammalian cells, the labeled lipid is also transferable to mammalian cells. Conversely, if the mammalian cell surface is radiolabeled (with 125I), the cell marker is in part transferable to the vesicles. Thus, interaction of mammalian cells with vesicles alters the characteristics of the cell in several ways. There is a loss of some cell surface components, a gain of vesicle lipid components, and an acquisition of intravesicular contents. Such alteration may affect the biological behavior of the cell in vivo. Thus, the in vivo distribution in the mouse of isologous red blood cells is altered after interaction with vesicles; the liver and spleen remove large proportions of such cells in comparison to control erythrocytes labeled with 51Cr. The behavior of vesicle survivors from a cell interaction is also altered. Upon reexposure of such vesicles to a fresh population of cells, the intravesicular marker is no longer transferable to cells; and upon injection of such vesicles into mice, the liver accumulation of vesicular label is reduced as compared with that of nonincubated vesicles. (Author Abstract)

99. EFFECT OF LIPOSOMES CONTAINING CHOLESTEROL ON THE ACTIVITY OF SOME SURFACE MEMBRANE ENZYMES OF MOUSE SPLEEN CELLS.

Deliconstantinos G
Dept. Physiology, Univ. Athens Medical Sch., Athens 609, Greece
IRCS Med Sci: Cancer; 8(7):493-494 1980

The effect of exogenous cholesterol (CHL) on the activities of two spleen lymphocyte surface bound enzymes, adenosine triphosphatase (Ecto-ATPase) and NAD splitting enzyme (NAD+ase), was investigated. Suspensions of spleen lymphocytes obtained from Swiss mice were incubated at 37 C for 2 hr with different amounts of liposomes composed of dipalmitoyl phosphatidyl choline (DPL) and [14C]-labeled CHL in a molar ratio of 1:2. Cells were separated from free liposomes by centrifugation, and uptake of [14C]-CHL by the cells was measured. Results indicated that the uptake of labeled CHL was proportional to the liposomal CHL concentration in a concentration range of 5 x 10(-5) M to 3 x 10(-4) M. The activity of Ecto-ATPase and NAD+ase in liposome-treated and untreated cell suspensions was measured after incubation for 30 min with appropriate substrates. Ecto-ATPase activity in suspensions of treated cells was 60% higher than that in suspensions of untreated cells, while NAD+ase activity in suspensions of treated cells was 40% lower than that in suspensions of untreated cells. No release of enzymes into the medium was detected during 30 min incubation with substrates. Both the uptake of CHL by liposome-treated cells and the resultant changes in the activity of surface bound enzymes were temperature dependent. Spleen cells incubated with liposomes containing only DPL showed no changes in Ecto-ATPase or NAD+ase activities. When liposome-treated cells were incubated with egg-lecithin liposomes to remove the added CHL, a statistically significant decrease of the Ecto-ATPase activity and an increase of the NAD+ase activity were observed. It is noted that Ecto-ATPase activity changes during malignant transformation. (12 Refs)

100. EFFECTS OF CHOLESTEROL-PHOSPHOLIPID LIPOSOMES ON THE TRANSFORMATION OF MOUSE SPLENIC LYMPHOCYTES BY LECTINS (MEETING ABSTRACT).

Ip SH, Abrahm J, Cooper RA
Hematology-Oncology Section, Univ. Pennsylvania, Philadelphia, PA, 19104
Biophys J; 25(2,part2):167a 1979

Mouse splenic lymphocytes were preincubated for 18 hr with sonicated dispersions of cholesterol and lecithin in a normal culture medium containing RPMI 1640 medium and 5% rat serum. The presence of cholesterol was found to enhance lectin-stimulatory effect. Little or no effect was observed when liposomes were added 24 or more hr after addition of lectin. The response was linearly related to the cholesterol/phospholipid (C/P) molar ratio of added liposomes with maximal stimulation at C/P greater than 1.0, no effect at a C/P of 0.2-0.4 and 30% inhibition at a C/P of 0.0. In contrast, a 25-fold variation in cholesterol concentration of the incubation medium at a constant C/P did not affect the degree of stimulation of the lymphocyte transformation. In addition to the enhanced transformation, DNA synthesis was greater in the cells preincubated with cholesterol. The max level of 3H-thymidine incorporation occurred 48 hr after the addition of concanavalin A (Con A) in the samples preincubated with cholesterol-enriched liposomes. The max in the control samples occurred at 72 hr. Similar results were observed with two different phospholipid liposomes (dipalmitoyl and egg lecithin), with three lectins (con A, phytohemagglutinin and pokeweed mitogen) and with either 3H-leucine or 3H-thymidine incorporation as the measure of transformation. 7-Ketocholesterol (2 ug/ml) suppressed the transformation in the control samples but had no effect on samples preincubated with cholesterol-enriched liposomes. These studies demonstrate that the lymphocyte transformation can be strongly influenced by cholesterol liposomes. The added cholesterol may have its effect by serving as a substrate for membrane biosynthesis or by altering the cellular membrane fluidity as demonstrated in our earlier studies. (no Refs)

101. THERMAL RESPONSIVENESS OF 3-HYDROXY-3-METHYLGLUTARYL-COENZYME-A REDUCTASE AND ACETYL-COENZYME-A CARBOXYLASE IN NEOPLASTIC GUINEA PIG LYMPHOCYTES (L2C).

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Unite de Recherches sur la Biochimie des Steroides, Unite 58 de l'Institut National de la Sante et de la Recherche Medicale, 60 Rue de Navacelles, F-34100 Montpellier, France
Eur J Biochem; 96(3):447-452 1979

The rate limiting enzymes of cholesterol and fatty acid biosynthesis, hydroxymethylglutaryl-CoA reductase and acetyl-CoA carboxylase, respectively, do not show equivalent thermal responsiveness in leukemic L2C guinea-pig lymphocytes. Both enzymes exhibit Arrhenius plots characteristic of membrane-association but hydroxymethylglutaryl-CoA reductase yields a single slope, compared with three slopes, crossing at 24 C and 12 C for acetyl-CoA carboxylase. Preincubation with phosphatidylcholine *liposomes* before enzyme assay does not modify the thermal behavior of acetyl-CoA carboxylase but introduces a discontinuity at 24 C in the Arrhenius diagram of hydroxymethylglutaryl-CoA reductase, conferring to this enzyme an activation energy close to that of normal cells. The Arrhenius plot for fatty acid biosynthesis in L2C cells parallels the thermotropism of the acetyl-CoA carboxylase with two discontinuities at 25 and 15 C. However, cholesterol biosynthesis shows a dis-

continuity at 24.6 C, whereas hydroxymethylglutaryl-CoA reductase activity does not. The different thermal behavior of hydroxymethylglutaryl-CoA reductase and acetyl-CoA carboxylase is discussed in terms of lipid heterogeneities in membrane enzyme environments, ie; enzyme localization in dissimilar lipid domains. We propose several hypotheses to account for the lack of correlation between the thermotropic responses of hydroxymethylglutaryl-CoA reductase activity and of cholesterol biosynthesis in L2C cells. (Author abstract) (34 Refs)

102. REGULATION OF CHOLESTEROL BIOSYNTHESIS BY NORMAL AND LEUKEMIC (L2C) GUINEA PIG LYMPHOCYTES.

Philippot JR, Cooper AG, Wallach DF
Tufts-New England Medical Center, Therapeutic Radiology Dept., Radiobiology Div., 171 Harrison Ave., Boston, MA 02111
Proc Natl Acad Sci USA; 74(3):956-960 1977

The mechanism(s) responsible for defective regulation of cholesterol biosynthesis in guinea pig leukemic (L2C) lymphocytes was investigated. L2C lymphocytes synthesize cholesterol at 30-40 times the rate for normal cells and fatty acids at 20-30 times the normal rate. The increased cholesterol synthesis correlates with an important enhancement of hydroxymethylglutaryl (HME)-CoA reductase activity and an accumulation of cholesterol in the cells. Exposure of L2C cells to *cholesterol/lecithin liposomes* did not depress their sterol biosynthesis. However, 25-hydroxycholesterol, an inhibitor of HMG-CoA reductase, and 25-hydroxycholecalciferol, a biologically potent form of vitamin D, blocked sterol biosynthesis of both normal and L2C lymphocytes. Both normal and L2C cells exchanged cholesterol equivalently with cholesterol/lecithin liposomes. The only difference in sterol biosynthesis observed between normal and L2C cells was in the temperature response of the enzyme. Arrhenius plots of this enzyme activity exhibited a prominent discontinuity at 24 C for normal cells but none for L2C. The activation energies for L2C cells and normal cells above the normal cell transition temperature were not significantly different. These data suggest that the defective regulation of cholesterol biosynthesis in L2C lymphocytes may derive from an abnormal constitution of their internal membranes. (30 Refs)

103. SURFACE MORPHOLOGY CHANGES IN LYMPHOCYTES INDUCED BY CHOLESTEROL DEPLETION (MEETING ABSTRACT).

Plesser YM, Polliack A, Doljanski F
Dept. Immunology, Hebrew Univ., Jerusalem, Israel
Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheba, 25-30 June, 1978. Ben Gurion University of the Negev, Beer Sheba, Israel, 347 pp., 1978.

Cholesterol is a characteristic component of mammalian cell surface membranes. Its role in membrane structure and function is just beginning to be elucidated. The aim of the present investigation was to see whether the cholesterol content of the lymphocyte membrane affects cell surface morphology. Surface membrane of peripheral blood lymphocytes and that of three lymphoid cell lines characterized by their markedly villous surface, were depleted of their cholesterol content, by interacting them with *lecithin liposomes*. The cells were incubated with the liposomes at 4 C or 37 C for 1-3 hr. This treatment caused a marked change in the microviscosity of the cell membrane. After treatment the cells were examined by scanning electron microscopy. The control lymphoid cells showed a typical villous surface morphology, whereas the liposome treated cells had smooth or folded surface membrane. Transmission electron microscopy showed that cells exhibiting these marked changes in surface topography were live and healthy. The role of cholesterol in controlling cell-surface morphology will be discussed. (no Refs)

104. EFFECT OF LIPOSOMES CONTAINING CHOLESTEROL ON ADENYLATE CYCLASE ACTIVITY OF CULTURED MAMMALIAN FIBROBLASTS.

Klein I, Moore L, Pastan I
Lab. Molecular Biology, NIH, NCI, Bethesda, MD, 20014
Biochim Biophys Acta; 506(1):42-53 1978

Liposomes prepared with cholesterol and dipalmitoyl phosphatidylcholine were incubated with a clone of normal rat kidney fibroblast cells in culture. The cells took up C14-cholesterol in proportion to the concentration of liposomes in the incubation medium, and the uptake increased with time over the 4 hr of study. Two cell membrane enzymes, adenylate cyclase and (Na+ + K+) ATPase, exhibited decreased activity after treatment with cholesterol-containing liposomes. The decrease in adenylate cyclase activity was directly proportional to the uptake of C14-cholesterol. When a variety of subclones of NRK 5W was examined, some were found to respond to cholesterol treatment and some did not. These data are consistent with the view that membrane cholesterol content plays a role in controlling the activity of some plasma membrane enzymes. (Author abstract) (34 Refs)

105. CONTROL OF IN VITRO CYTOTOXICITY OF POSITIVELY CHARGED LIPOSOMES.

Panzner EA, Jansons VK
Dept. Microbiology, Coll. Medicine Dentistry, New Jersey Medical Sch., 100 Bergen St., Newark, NJ, 07103
J Cancer Res Clin Oncol; 95(1):29-37 1979

The parameters which influence the in vitro cytotoxicity of positively charged liposomes for L 1210 cells were analyzed. The cytotoxicity was liposome/cell ratio-dependent. It also depended upon the mole fractions of stearylamine (SA) to phosphatidylcholine (PC). There was no difference between the cytotoxicity of unilamellar and multilamellar vesicles but the cytotoxic effect of free SA was about 4 x greater than that of liposome incorporated SA at a molar ratio of 1:4, SA:PC, respectively. The process which resulted in cell death was irreversible after 60 min of cell-liposome contact. The simultaneous presence of neutral liposomes or of positively charged liposomes with a lesser charge density decreased the cytotoxic effect of liposomes with a higher SA content. The cytotoxicity could be deceased by trypsinization of cells following exposure to liposomes while treatment of cells with trypsin prior to the exposure to positvely charged liposomes had no effect on the subsequent cytotoxicity. The cytotoxicity was also decreased if cells were incubated in the presence of sodium azide. The usual concentration of serum (10%) present in the growth medium had no effect on the cytotoxicity while preincubation of cells with liposomes in 80% serum resulted in full protection. The protective effect of serum could be replaced by the albumin fraction. (Author abstract) (15 Refs)

106. THE EFFECT OF BUTYRATE ON GLYCOSPHINGOLIPID METABOLISM IN HUMAN EPIDERMOID CARCINOMA (KB) CELLS (MEETING ABSTRACT).

Lockney M, Moskal JR, Fung YK, Macher BA
Dept. Biochemistry, Michigan State Univ., E. Lansing, MI, 48824
Fed Proc; 37(6):1766 1978

Experiments were performed to ascertain whether glycosphingolipid metabolic changes accompany butyrate treatment of KB cells and the significance of such phenomena. Cytosine monophosphate-NAN:lactosylceramide sialyltransferase was stimulated (9-fold) in the presence of butyrate (2-4 milliM, 15-24 hr preincubation). An alpha-galactosyltransferase, uridine diphosphate (UDP)-galactose(Gal):lactosylceramide galactosyltransferase (GalT-1), and a beta-galactosyltransferase, UDP-Gal:neolactotetraose galactosyltransferase (GalT-2), were also detected in both control and butyrate treated cells. Butyrate treatment affected GalT-1 (50% inhibition), whereas GalT-2 activity was not changed markedly by butyrate but was 10-fold higher than GalT-1 in both control and butyrate treated cells. Cell surface labeling studies showed that GM3 was exposed to a greater extent (2-fold) in butyrate vs control cells. *Liposomes* prepared with or without GM3 did not cause morphological changes or inhibit butyrate induced process formation. However, pretreatment of cells with phosphatidylcholine liposomes (PCL) followed by butyrate caused a significant decrease in thymidine uptake compared to butyrate or butyrate followed by PCL treatment. Examination of glycosyl hydrolases showed a significant increase in beta-N-acetylhexosaminidase activities in butyrate treated cells. Culture medium from butyrate treated cells was found to have approx 50% less beta-N-acetylglucosaminidase activity when compared to controls. Thymidine uptake studies suggest that butyrate may be synchronizing KB cells in the G1 phase of the cell cycle.

107. CYTOTOXICITY OF LIPOSOMES TOWARDS CULTURED HUMAN AND RAT BLADDER CANCER CELL LINES (MEETING ABSTRACT).

Behrens BC, Yamamoto N, Brown RR, Bryan GT
Dept. Human Oncology, Univ. Wisconsin Center for Health Sciences, Madison, WI, 53792
Proc Am Assoc Cancer Res; 20:160 1979

We studied the cytotoxicity of liposomes, phospholipid vesicles of potential use as vehicles for the delivery of chemotherapeutic agents, against cultured human (RT4 and 647U) and rat (R4909) bladder cancer cell lines. Sterile multilamellar liposomes were formed in 10 milliM phosphate buffer (pH 7.4) and composed of phosphatidylcholine (PC), cholesterol (C), stearylamine (SA) and diacetyl phosphate (DCP) at molar ratios of 7 PC/1 C (neutral charge), 7 PC/1 C/2 SA (positive charge), and 7 PC/1 C/2 DCP (negative charge). These preparations were tested against the above cell lines grown as monolayers in minimal essential medium supplemented with L-glutamine, fetal calf serum, and antibiotics. Cells were plated at a density of 1-3 x 10(5) cells/well and grown in a humidified 5% CO2 atmosphere. Varying doses of liposomes were added for 1-24 hr 1 day later, and cell survival then indirectly measured by neutral red dye uptake 2 days after plating. Cytotoxicity was dose related and in the relative order of (+) charged greater than (-) charged greater than neutral liposomes for all cell lines. Total lipid doses of 0.1 to greater than 26 umole (uMol)/well were required to limit cell growth to 10% of control with 24 hr of treatment, depending on liposome charge and cell line. Growth of all cell lines was limited to 10% of control with 1-4 hr of treatment with 9 uMol total lipid/well of (+) charged liposomes. Neither sonication (3 hr) nor exposure of liposomes to air (24 hr) before their use significantly altered cytotoxicity of (+) charged liposomes. Liposomes, rather than serving as inert vehicles for drug delivery, thus display dose- and charge-related cytotoxicity towards cultured bladder cancer cell lines. (no Refs)

108. LIPID VESICLE INTERACTION WITH EMT-6 TUMOR CELLS AND EFFECT ON SUBSEQUENT CELL GROWTH.

Dunnick JK, Kallman RF, Kriss JP
Natl. Inst. Allergy Infectious Diseases, NIH, Bethesda, MD
Biochem Biophys Res Commun; 73(3):619-624 1976

Interaction of lipid vesicles with EMT-6 mammary sarcoma cells is described, as is the effect on the ability of these cells to grow in an in vitro tissue culture assay system. EMT-6 cells were incubated with lipid vesicle preparations of varying composition, after which cell viability was determined. When cells were preincubated with artificial lipid vesicles formed from phosphatidylcholine, gangliosides, and cholesterol, lipid exchange between cell and vesicle did occur, but the exchange had no detectable effect on cell growth. However, growth of cells was reduced when they were preincubated with vesicles containing stearylamine or phosphatidylserine to 66% and 28% of control, respectively. Cell permeability was not affected by incubation of EMT-6 cells with vesicles or lipids alone. These and other data indicate that the potential exists to deliver growth inhibiting compounds to tumor cells in vivo by carrying these substances in lipid packages. (22 refs)

109. LIPOSOME-INDUCED MORPHOLOGICAL DIFFERENTIATION OF MURINE NEUROBLASTOMA.

Chen JS, Del Fa A, Di Luzio A, Calissano P
Laboratorio Biologia Cellulare CNR, Via G. Romagnosi, 18A, Rome, Italy
Nature (Lond); 263(5578):604-606 1976

The carrier in the nerve growth factor (NGF) induction of morphological differentiation in NB41A3 cells was investigated. The optimum conditions for max binding were first investigated. A mixture of sonicated PC-PS 10:1.5 (w/w) liposomes progressively attached to and/or penetrated the cell membrane during a 24 hr incubation period at 37 C. Addition of cholesterol to the lipid suspension did not significantly change the binding pattern. Changing the net charge of the liposome from negative to positive by introducing stearylamine severely reduced the viability of the NB cells. The fine structure of liposome-induced processes indicated an abundance of microtubules in parallel arrays and other fibrillar structures tentatively identified as microfilaments. Further studies indicated that liposome-induced morphological differentiation is accompanied by a concomitant inhibition of cell division; it is not known if these phenomena are related. Only dibutyryl cyclic AMP induced process formation, but not to the same extent as the liposomes; papaverine, 5-bromodeoxyuridine, and dimethylsulfoxide had little or no effect. Using C14-PC-loaded liposomes, 2-4 nanomoles of liposomes bound to or penetrated the cells corresponding to an av of 3 x 10(8) phospholipid molecules per neuroblastoma cell. It remains to be determined to what extent in vitro process formation in NB cells is a true morphological sign of neural differentiation.

110. LECTIN-INDUCED CELL AGGLUTINATION AND MEMBRANE CHOLESTEROL LEVELS.
Alderson JC, Green C
Environmental Safety Div., Unilever Res., Colworth/Welwyn Lab., Colworth House, Sharnbrook, Bedford, MK 44 1LQ, England
Exp Cell Res; 114(2):475-479 1978

The effects of membrane cholesterol levels on lectin-induced cell agglutination were studied in human and guinea pig RBC and in Ehrlich ascites carcinoma cells. The membranes were enriched or depleted of cholesterol by in vitro incubation with phosphatidylcholine or phosphatidylcholine/cholesterol *liposomes*. Ehrlich ascites cells were also enriched with an extra sterol shown to be present in the plasma membrane. Following incubation of the cells with cholesterol-containing liposomes, the plasma membrane cholesterol level increased by approx 40%. Enrichment of the cells with cholesterol made them less susceptible to agglutination by concanavalin A (Con A) or phytohemagglutinin (PHA), while depletion of membrane cholesterol increased susceptibility to agglutination by plant lectins. It was suggested that the alterations in surface membrane sterol levels are followed by changes both in short-range movement of individual receptor molecules and in cell shape and deformability which control the agglutinability of the cells. (32 Refs)

111. EFFECT OF LIPID VESICLES ON THE GROWTH OF EHRLICH ASCITES CARCINOMA IN MICE.
Sur P, Hazra B, Roy DK
Dept. Pharmacy, Jadavpur Univ., Calcutta 700032, India
IRCS Med Sci: Cancer; 7(9):453 1979

The effect of different types of lipid vesicles on the growth of Ehrlich ascites carcinoma (EAC) in male Swiss albino mice was studied. Negatively-charged and neutral liposomes inhibited the growth of EAC in vivo with respect to saline, whereas positively-charged liposomes markedly enhanced the growth of tumor cells. (5 Refs)

V. IN VITRO EVALUATIONS OF LIPOSOMES AS CARRIERS OF DRUGS AND OTHER SUBSTANCES

A.

In vitro studies with liposome-encapsulated antitumor agents

112. ROLE OF CHOLESTEROL IN ENHANCING THE ANTITUMOR ACTIVITY OF CYTOSINE ARABINOSIDE ENTRAPPED IN LIPOSOMES.
Mayhew E, Rustum YM, Szoka F, Papahadjopoulos D
Dept. Experimental Pathology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Treat Rep; 63(11/12):1923-1928 1979

Studies were carried out to determine whether there was any correlation between liposome composition, permeability of entrapped drug, and antitumor activity against mouse L1210 leukemia. These studies were done using reverse evaporation phase liposomes composed of the phospholipids phosphatidylglycerol (PG) and phosphatidylcholine (PC) in a constant molar ratio (1:4) and with varying amounts of cholesterol (Chol). The results indicated that with increasing amounts of Chol present in the liposomes (from a total absence of Chol to a molar ratio of 1:4:5 of PG:PC:Chol) the rate of leakage of cytosine arabinoside (ara-C) was markedly reduced. At 24 hr following in vitro incubation of liposomes containing entrapped ara-C in the presence of 80% fetal calf serum, the amount of ara-C remaining associated with the liposomes was 72% with liposomes composed of PG:PC:Chol (at ratios of 1:4:5) but was reduced to 12% with liposomes composed of only PG:PC (at ratios of 1:4). Furthermore, increased molar ratios of Chol:phospholipid correlated with an increase in the antitumor activity by ip injection against ip inoculated mouse L1210 leukemia. Significant numbers of mice surviving 30 days were observed only when Chol was present in PG:PC:Chol ratios of 1:4:3 and 1:4:5. These results suggest that reverse evaporation phase liposomes can be made which are relatively impermeable in serum by manipulation of the Chol:phospholipid ratio and thus can be relatively stable in biologic fluids. In addition, the results indicate that the antitumor activity of the entrapped drug is inversely related to its permeability through the liposome membrane. (Author abstract) (22 Refs)

113. IN VITRO CYTOTOXICITY OF CYTOSINE ARABINOSIDE ENTRAPPED IN PHOSPHOLIPID VESICLES (MEETING ABSTRACT).
Mayhew E, Papahadjopoulos D
Dept of Experimental Pathology, Roswell Park Memorial Inst, Buffalo, N.Y. 14263.
Proc Am Assoc Cancer Res; 18:110 1977

The anti-leukemic drug cytosine arabinoside (ARA-C) and some phosphorylated derivatives were entrapped in a series of different types of phospholipid vesicles. Comparisons were made between the effectiveness of the drug entrapped in these vesicles against L1210, ELD ascites, 3T3 SV40 transformed cells in vitro, compared to the 'free' drug and to the 'free' drug used in combination with non-drug containing vesicles. The different vesicles used were positively or negatively charged, fluid or solid, multilamellar or small (<1000 A diameter) and large unilamellar (>1000 A). Different vesicle drug combinations gave a ID50 somewhat different from the value for the free drug. ARA-C entrapped in positively charged fluid small and unilamellar vesicles was 2-3 times more effective than the free drug. ARA-CTP, presumably the biologically active moiety of ARA-C, when entrapped, particularly in positively charged vesicles was effective at concentrations considerably less than that required for the free ARA-CTP indicating that the highly charged molecule when entrapped, indeed got transported across the membrane barrier, without degradation. (Author Abstract)

114. INHIBITION OF CELLULAR GROWTH AND DNA SYNTHESIS BY 5'-FATTY DERIVATIVES OF 1-BETA-ARABINOFURANOSYL CYTOSINE (ARA-C) INCORPORATED INTO LIPOSOMES (MEETING ABSTRACT).
Dorsa MJ, Magee W
Div. Allied Health and Life Sciences, Univ. Texas, San Antonio, TX, 78285
Fed Proc; 37(6):1309 1978

Several 5'-fatty acid derivatives of ARA-C were incorporated individually into positively charged multilamellar vesicles (MLV) of sphingomyelin: cholesterol: stearyl amine in the weight ratios of 43: 8: 6 mg. The fatty acid side chain served to anchor the derivative by insertion into the phospholipid bilayer of the MLV. From 56-90% of the added derivatives remained in stable association with the MLV.

The drug-containing MLV's were found to be potent inhibitors of cellular growth and division when tested in a microtiter plate test system using L 929 mouse fibroblast cells. Dose response curves were obtained for each preparation and showed that the order of activity was lauroyl greater than benzoyl greater than anisoyl greater than palmitoyl greater than octanoyl ARA-C. Equivalent amounts of ARA-C derivatives giving a 50% inhibition in increase in cell numbers ranged from 0.02 to 0.4 microg/ml from the most to the least active MLV. These MLV also were potent inhibitors of phytohemagglutinin stimulated DNA synthesis in normal human lymphocytes. Further studies will be extended to examine tumor inhibition in test animals.

115. SPECIFIC INTERACTION OF MYELOMA TUMOR CELLS WITH HAPTEN-BEARING LIPOSOMES CONTAINING METHOTREXATE AND CARBOXYFLUORESCEIN.

Leserman LD, Weinstein JN, Moore JJ, Terry WD
Centre d'Immunologie INSERM-CNRS, Marseille-Luminy, Case 906, F-13288 Marseille, France
Cancer Res; 40(12):4768-4774 1980

Hapten-bearing liposomes containing methotrexate and the fluorescent solute carboxyfluorescein were incubated with murine myeloma tumor cells expressing surface immunoglobulin with affinity for the hapten. Liposomes bearing the dinitrophenyl hapten became bound to MOPC 315 myeloma tumor cells, and liposomes bearing the phosphorylcholine hapten became bound in much larger amounts to TEPC 15 cells. In each case, fluorescence microscopy showed a patchy surface pattern, indicating intact liposomes at the cell surface. Few liposomes were bound to cells in the presence of excess soluble hapten or to cells lacking the relevant surface immunoglobulin. Cell-associated liposomes were quantitated by use of the fluorescence-activated cell sorter, and the pharmacological effect of the methotrexate was assessed from measurement of incorporation of radiolabeled deoxyuridine into the cells. Little inhibition of deoxyuridine incorporation was observed, because contents of the bound liposomes did not enter the cytoplasmic compartments of the cells. (Author abstract) (36 Refs)

116. RECEPTOR-MEDIATED ENDOCYTOSIS OF ANTIBODY-OPSONIZED LIPOSOMES BY TUMOR CELLS.

Leserman LD, Weinstein JN, Blumenthal R, Terry WD
Centre d'Immunologie Institut National de la Sante, Case 906, 13288 Marseille Cedex 2, France
Proc Natl Acad Sci USA; 77(7):4089-4093 1980

Specific receptor-mediated delivery of the contents of small, sonicated liposomes was studied with three murine tumor cell types: an IgG Fc receptor-negative nonphagocytic line (EL4); an Fc receptor-positive phagocytic line (P388D1); and an Fc receptor-positive nonphagocytic line (P388). The liposomes (formed from phosphatidylcholines, cholesterol, and dinitrophenyl-substituted phosphatidylethanolamine) contained carboxyfluorescein as a fluorescent marker and methotrexate as a pharmacologic agent. Binding and internalization of the liposomes were observed by fluorescence microscopy and measured by flow microfluorometry. The hapten-derived lipid was used as a binding point on the liposome for the antibody-combining site of the immunoglobulin. In the presence of IgG anti-dinitrophenyl, but not F(ab')2 or IgA anti-dinitrophenyl, liposomes bound to the Fc receptor-bearing cells. The liposomes underwent endocytosis by the P388D1 cells and, to a lesser extent, by the P388 cells. As measured by depression of [3H]deoxyuridine incorporation, methotrexate in IgG-opsonized liposomes had a much greater pharmacologic effect on the P388D1 cells than did the same amount in unopsonized liposomes or in free soln. This observation indicates that an appropriately chosen drug, incorporated in liposomes, can exert its effect on the cytoplasmic target after endocytosis. P388 cells showed a moderate effect of the drug in liposomes. Neither P388 nor P388D1 cells bound or ingested unopsonized liposomes, and the Fc receptor-negative EL4 line neither bound nor ingested opsonized liposomes. The data demonstrate specific interaction of opsonized liposomes with the cells' IgG Fc receptor. (Author abstract) (24 Refs)

117. ALTERATIONS OF THE CARRIER-MEDIATED TRANSPORT OF AN ANIONIC SOLUTE, METHOTREXATE, BY CHARGED LIPOSOMES IN EHRLICH ASCITES TUMOR CELLS.

Fry DW, White JC, Goldman ID
Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
J Membr Biol; 50(2):123-140 1979

Interaction of positively charged liposomes with Ehrlich ascites tumor cells increases the bidirectional transmembrane fluxes of the anionic folic acid analog, methotrexate. Negative liposomes reduce methotrexate influx. Stimulation of methotrexate influx by positively charged liposomes is time and concentration dependent, requiring at least a 5 min incubation with 2.5 milliM (mM) phosphatidylcholine containing 20% stearylamine for max effect. Stimulation is not appreciably reversed by washing the cells. Similar increases are observed for influx and efflux so that there is no change in the steady state methotrexate electrochemical potential difference across the cell membrane. The increase in influx appears to be a stimulation of the carrier-mediated transport process for methotrexate since both control and stimulated influx are abolished by the competitive inhibitor, 5-formyltetrahydrofolate or the sulfhydryl group inhibitor, p-chloromercuriphenylsulfonic acid and the Q10 of the system remains unchanged. Influx of 5-methyltetrahydrofolate, which shares the same transport carrier as methotrexate, is also stimulated. However, the transport of folic acid, which is structurally similar to methotrexate but does not utilize the carrier, is unaffected. The kinetic change induced by positively charged liposomes is an increase in the max influx velocity while the influx time constant remains unchanged. Transstimulation of methotrexate influx by 5-formyltetrahydrofolate occurs to the same extent in the presence or absence of positively charged liposomes. The liposomes have no apparent effect on the intracellular water, the extracellular space, or the chloride distribution ratio. The data suggest that interaction of positively charged liposomes with Ehrlich ascites tumor cells accelerates the rate of transposition of the membrane carrier system for methotrexate, altering the kinetics of transport without a change in transport thermodynamics. (Author abstract) (49 Refs)

118. LIPOSOME-ENCAPSULATED METHOTREXATE INTERACTIONS WITH HUMAN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS.

Todd JA, Levine AM, Tokes ZA
Dept. Biochemistry, Univ. Southern California Sch. Medicine, 1303 North Mission Road, Los Angeles, CA, 90033
JNCI; 64(4):715-719 1980

The uptake of free and liposome-entrapped methotrexate (MTX) by human chronic lymphocytic leukemia cells was compared under incubation conditions resembling those encountered in vivo. Liposome encapsulation enhanced up to 200x the association of MTX with these cells. Autoradiographic studies established an association of [3H]MTX liposomes with the cells. Such a mode of delivery did not sig-

nificantly increase the amount of drug available to inhibit dihydrofolate reductase, which suggested that the liposome content was not readily available to the cytoplasmic sites of action. Increased doses of encapsulated MTX resulted in enzyme inhibitions that were similar to those obtained with the free drug. This finding demonstrates that higher doses of MTX delivered by liposomes could be potentially useful in overcoming drug-transport resistance. (Author abstract) (24 Refs)

119. INCREASED UPTAKE OF LIPOSOME ENTRAPPED METHOTREXATE BY CHRONIC LYMPHOCYTIC LEUKEMIA CELLS (MEETING ABSTRACT).

Todd JA, Levine AM, Tokes ZA
Dept. Biochemistry and Hematology, LAC/USC Cancer Center, USC Sch. Medicine, Los Angeles, CA, 90033
Fed Proc; 37(6):1543 1978

Human lymphocytes, isolated from patients with chronic lymphocytic leukemia (CLL) were incubated in the presence of the patient's plasma with unilamellar cationic (phosphatidyl choline, cholesterol, octadecylamine; 7:2:0.5) or neutral (phosphatidyl choline, cholesterol; 7:2) liposomes containing 3H-methotrexate (MTX). A 20 to 200 fold increase in cell associated MTX was observed with liposomes as compared to the incubation with free drug. 2.8 to 5.6 microg of free or liposome encapsulated MTX was added to 0.5 ml of patient plasma, containing 2.5 x 10(7) purified and viable lymphocytes and incubated at 37 C. The uptake was time dependent. 10-50% of the liposome encapsulated MTX was released from the cells after 1 hr treatment with 0.25% trypsin indicating some passive adsorption to the cell surfaces. Conversely, no MTX was released after trypsinization of lymphocytes which had been incubated with free MTX. MTX is not usually used in CLL therapy. However, there is recent evidence to suggest that MTX, when used in very high dosage levels, may be quite effective in the treatment of lymphocytic lymphomas, which are related disorders. The use of liposome entrapped MTX, resulting in increased uptake of drug by the malignant cell population, may prove to be an effective method of treating lymphoma, while avoiding potential side effects of high dosage MTX therapy. (no Refs)

120. EVIDENCE FOR BIDIRECTIONAL FLUXES OF METHOTREXATE IN EHRLICH ASCITES TUMOR CELLS MEDIATED BY THE SAME CARRIER (MEETING ABSTRACT).

Fry DW, Lawrence W
Dept. Medicine, Medical Coll. Virginia, Richmond, VA, 23298
Proc Am Assoc Cancer Res; 21:21 1980

Two lines of evidence suggest bidirectional fluxes of methotrexate (MTX) in Ehrlich ascites tumor cells are mediated, at least in part, by a single carrier. First, (3H)MTX influx is stimulated in cells preloaded with nonlabeled MTX when equilibrated in a high K+, low Na+ buffer. This trans-stimulation during autoexchange provides firm evidence for a shared carrier under these conditions. The basis for the emergence of trans-stimulation in high K+ buffer is unclear, but may be due to K+-induced alterations in the microenvironment of the carrier which enhances its mobility in the loaded state and possibly results in depolarization of the cells. The second line of evidence is derived from symmetrical alterations in bidirectional fluxes of MTX when cells are exposed to charged liposomes. Positively charged liposomes composed of phosphatidylcholine (PC) and stearylamine stimulate both influx and efflux of MTX while negatively charged liposomes composed of PC and stearic acid inhibit bidirectional flows. The symmetry of these alterations is consistent with the absence of any effect by these liposomes on the intracellular concentration of MTX at the steady state. This effect is specific for the MTX-tetrahydrofolate cofactor carrier since the stimulated influx is abolished by 5-CHO-H4-folate and mercurials. Further evidence for carrier specificity is that positive liposomes also stimulate influx of 5-CH3-H4-folate and aminopterin, but do not affect transport of folic acid which does not utilize the MTX carrier. While it is possible that efflux of MTX is mediated partially by a carrier distinct from influx, these data suggest that bidirectional flows can occur, at least in part, by the same mechanism. (no Refs)

121. POSITIVELY CHARGED LIPOSOMES SPECIFICALLY ENHANCE THE CARRIER-MEDIATED TRANSPORT OF THE BIVALENT ANION, METHOTREXATE (MTX), IN THE EHRLICH ASCITES TUMOR CELL (MEETING ABSTRACT).

Fry DW, Courtland J, Goldman ID
Medical Coll. Virginia, Richmond, VA, 23298
Fed Proc; 38(3,part2):887 1979

Positively charged (+) liposomes, composed of phosphatidylcholine (PC) and stearylamine (SA), stimulate influx of methotrexate by 2-3 fold. Negatively charged (-) liposomes composed of PC and dicetylphosphate (DCP) inhibit influx. Stimulation exhibits a lag phase (approx 5 min) and depends on liposome concentration. Influx and efflux are symmetrically increased without change in the steady-state transcellular MTX electrochemical-potential difference. Stimulation is specific for the transport carrier since (1) both control and stimulated influx are abolished by 5-formyltetrahydrofolate or p-chloromercuriphenylsulfonic acid (agents which block the carrier-mediated flux); (2) the Q10 of the stimulated and control fluxes are the same; and (3) transport of folic acid which is similar in structure and charge, but not transported by the carrier, is unaffected by (+) liposomes. The change in influx kinetics induced by (+) liposomes is an increase in Vmax while the Km remains unaltered. Liposomes do not alter the intracellular water, inulin space, chloride distribution ratio or Trypan blue exclusion. These data suggest that (+) charged liposomes stimulate the rate of transposition of the membrane carrier for MTX altering the kinetics of transport without a change in transport thermodynamics. While the mechanism is unclear, possibilities include changes in membrane fluidity or selective permeability in the vicinity of the transport carrier. (no Refs)

122. ACTIVATION IN VITRO OF NITROGEN MUSTARD BY LIPOSOMAL TRANSPORT.

Rutman RJ, Avadhani NG, Ritter C
Dept. Animal Biology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA 19174
Biochem Pharmacol; 26(1):85-88 1977

The effect of a hydrophobic carrier (liposomes) on nitrogen mustard (HN2) action was studied, since the marked contrast between mitochondria exposed to HN2 in vivo and in vitro suggests a difference in permeability to HN2 under the two conditions. Sonicates were prepared (10 mg/ml L-a-lecithin in 0.9% NaCl) and mixed with equimolar concentrations of HN2, based on phospholipid (PL). A 10**-5 M HN2-PL combination produced an almost complete inhibition of the biosynthetic activity of RNA and protein synthesis. The activity of HN2-PL against isolated mitochondria was several times greater than that of HN2 alone in vitro and 10-100 times greater than that of HN2 alone in vivo. Specific permeability changes are presently being studied

since the evidence for the in vivo potentiation of drug action by liposomes makes such permeability changes a possible explanation for the effects of phospholipid on HN2. (11 refs)

123. EFFECT OF PHOSPHOLIPIDS ON MAINTENANCE OF THE CYTOTOXICITY OF 1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA IN AQUEOUS SUSPENSION.

Maker HS, Syed HH, Lehrer GM
Dept. Neurology, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029
JNCI; 60(5):1055-1057 1978

The effects of phosphatidyl serine (PS), phosphatidyl ethanolamine (PE), or phosphatidyl choline (PC) on the cytotoxicity of lomustine (CCNU) were studied. CCNU (2.0 milliM) was incubated with a polar glycerophospholipid (0.5 mg/ml) for up to 6 hr, then added to cultures of C-6 glioma cells (final concentration, 100 uM). When CCNU was preincubated in phosphate buffered saline, cytotoxicity decreased markedly after 1 hr and disappeared after 6 hr. The addition of PC significantly prolonged the duration of action of CCNU (p less than 0.01). Medium (alone or with serum), PS, and PC were less active in preserving the cytotoxicity of CCNU. This preservation of cytotoxicity may have been caused by the formation of common micelles between CCNU and the phospholipid. The importance of lipid interactions to the effectiveness of the nitrosoureas in vivo is unknown, but such interactions might be important to the duration of action of these agents, their penetration of the blood-brain barrier, and their attachment to cell membranes. (15 Refs)

124. USE OF LIPID VESICLES AS CARRIERS TO INTRODUCE ACTINOMYCIN D INTO RESISTANT TUMOR CELLS.

Papahadjopoulos D, Poste G, Vail WJ, Biedler JL
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263
Cancer Res; 36(9):2988-2994 1976

RNA synthesis is extremely sensitive to inhibition by actinomycin D (AD) in Chinese hamster DC-3F cells, derived from a lung fibroblast population; 250 times more AD was required to inhibit RNA synthesis in the AD-resistant subline DC-3F/ADX. Incubation of DC-3F/ADX cells in a medium containing various concentrations of AD contained within lipid vesicles resulted in a 200-fold increase in sensitivity to AD; the dose-response curve was very similar to that of the parent line exposed to free AD. Measurement of 3H-AD uptake by the resistant cells in the presence of lipid vesicle containing AD indicated an approx 5 x increased uptake compared to cells exposed to free AD. The vesicles themselves had no inhibitory effect on RNA synthesis, nor did vesicles without entrapped AD + free AD increase the inhibition seen with free AD alone. The dosage required to produce 50% inhibition of growth (ED50) of DC-3F cells was 0.004 ug/ml of AD, compared to the ED50 for the AD-resistant line of 7.2 ug/ml. The ED50 for the resistant cells in the presence of AD entrapped in lipid vesicles was 0.06 ug/ml, a 120-fold increase in sensitivity compared to the resistant cells exposed to free AD. The results support the hypothesis that cellular resistance to AD is due to a lowered capacity to take up actinomycin D as a result of a reduction in the permeability of the cellular plasma membrane to AD. The potential value of using lipid vesicles to introduce other classes of drugs into cultured cells and the possible chemotherapeutic application are discussed. (42 refs)

125. DRUG-CONTAINING LIPID VESICLES RENDER DRUG-RESISTANT TUMOUR CELLS SENSITIVE TO ACTINOMYCIN D (LETTER TO EDITOR).

Poste G, Papahadjopoulos D
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263
Nature (Lond); 261(5562):699-702 1976

A new method is reported for enhancing drug uptake by drug-resistant cells. The method uses lipid vesicles as carrier agents to introduce actinomycin D (AD) directly into cells. The AD-resistant Chinese hamster cell line, DC3F-ADX, was grown routinely in Eagle's minimum essential medium containing AD at 10 ug/ml, but was grown in medium without AD for 10 to 15 days before use in experiments. Vesicles were prepared from a lipid mixture containing 1 umole of phosphatidylserine, 9 umole of phosphatidylcholine, and 10 umole of cholesterol which were mixed in chloroform, evaporated to dryness in a vacuum and suspended in 1.0 ml of calcium- and magnesium-free phosphate-buffered saline containing different concentrations of AD. When the starting AD concentration in buffer was 17 ug/ml or less, approx 60% of available drug was captured by the vesicles. Treatment of replicate populations of resistant cells with vesicles containing different concentrations of AD resulted in inhibition (> 75%) of cellular RNA synthesis at a drug concentration of 0.25 ug/ml, a 200-fold decrease of the concentration of free drug needed to produce the same effect. In addition, the concentration of AD needed to reduce cell growth to 50% of that occurring in untreated control cultures was reduced from 7.2 ug/ml for cells exposed to free AD to 0.062 ug/ml for cells treated with AD-vesicles. Vesicle uptake per se failed to alter significantly the transfer of free AD across the cellular plasma membrane. Lipid vesicles might be used to enhance the uptake of other cytostatic and cytotoxic drugs by resistant tumor cells, thus providing a possible novel approach for cancer chemotherapy in vivo. (21 refs)

126. EVIDENCE OF A COMPLEX BETWEEN ADRIAMYCIN DERIVATIVES AND CARDIOLIPIN: POSSIBLE ROLE IN CARDIOTOXICITY.

Goormaghtigh E, Chatelain P, Caspers J, Ruysschaert JM
Laboratoire de Chimie Physique des Macromolecules aux Interfaces, Universite Libre de Bruxelles, C. P. 206/2, Boulevard du Triomphe, 1050 Bruxelles, Belgium
Biochem Pharmacol; 29(21):3003-3010 1980

Most of the mitochondrial damage induced by antimitotic drugs of the adriamycin family could be due to the high affinity of these drugs for the membrane. The prime interaction between the anthracycline drug and this membrane would explain specific alterations observed on mitochondria. Cardiolipin has been proposed as a privileged target. We have tested this hypothesis here. *Model membranes (lipid monolayers, liposomes)* were used to demonstrate the interaction between these anthracycline drugs and different phospholipids. A new surface potential technique showed the specificity of adriamycin derivatives for cardiolipin whereas no complexation was observed with neutral phospholipids (dipalmitoyl lecithin and egg lecithin). Association constants were evaluated and a good correlation was obtained between the mitochondrial toxicity of each drug and its affinity for cardiolipin. Fluorescence measurements were carried out in order to locate precisely the position of the drug in the lipid bilayer. Perturbations of the lipid organization after complex formation were analyzed using phospholipase A2 as an enzymic probe. (Author abstract) (38 Refs)

127. REDUCTION OF INHIBITORY EFFECT OF ADRIAMYCIN ON MYOCARDIAL CONTRACTION IN VITRO BY ENTRAPMENT IN LIPOSOMES (MEETING ABSTRACT).

Maslow DE, Mayhew E, Olson F, Rustum Y
Roswell Park Memorial Inst., Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 21:281 1980

The dose dependent cardiac toxicity of anthracyclines such as adriamycin (AM) limits the clinical utility of these agents. Complexing of AM to macromolecular carriers such as liposomes or DNA has been suggested as a means of reducing cardiac toxicity by limiting drug uptake. Attempts have been made to develop methods for the preparation of reproducible, stable AM-liposomes of different composition and of narrow size distribution. These liposomes, composed of charged or neutral phospholipids in combination with cholesterol, are true spherical liposomes up to a M ratio of approx 1 AM to 10 phospholipid. The myocardial cell contraction rate (MCCR) of cultured isolated chick embryonic heart cells was used as an in vitro assay for investigation of the effects of free AM, non-AM containing liposomes and AM-entrapped in liposomes. The results indicate that positively charged liposomes were much more toxic than neutral or negatively charged liposomes at equivalent lipid concentrations. Negative and neutral liposomes were not toxic below approx 10(-3) M lipid. 'Free' AM at 10(-5) M stopped MCCR and at 10(-6) M significantly reduced MCCR. However, when AM was entrapped in neutral or negative liposomes, the MCCR was only reduced slightly at 10(-5) M AM and there was no effect at 10(-6) M. In vivo studies have shown that entrapment of AM in liposomes does not modify the drugs' antitumor activity in mice bearing B16 melanoma, Lewis lung carcinoma or L1210 leukemia. These results indicate that AM entrapment in negative and neutral liposomes produced less acute cardiac toxicity than free AM against chick embryonic heart cells in vitro suggesting the use of these liposomes in reducing cardiac toxicity in vivo. (no Refs)

128. THE ACCUMULATION BY FIBROBLASTS OF LIPOSOMALLY ENCAPSULATED VINBLASTINE.

Layton D, De Meyere J, Collard M, Trouet A
International Inst. Cellular and Molecular Pathology, Ave. Hippocrate, 75, Bruxelles 1200, Belgium
Eur J Cancer; 15(12):1475-1483 1979

Vinblastine, an anti-mitotic agent, was entrapped in liposomes prepared from phosphatidylcholine, cholesterol, and stearylamine (mole ratio 7:2:1), and such liposomes incubated with cultured rat embryo fibroblasts. The fibroblasts accumulated the liposomally encapsulated vinblastine in a markedly different manner to that observed for the free agent. In the former case there was an initial high rate of drug uptake followed by a linear accumulation, which was parallel to that of a liposomal membrane marker and although the ratio of accumulated vinblastine to lipid was different to that pertaining to the original preparation prior to incubation, the ratio did remain constant over the linear phase of accumulation. The effect upon the accumulation of incubation temperature and of release experiments indicated that the mechanism of uptake of a liposomally encapsulated drug by fibroblasts was complex, possibly involving a combination of adsorption and endocytosis. (Author abstract) (30 Refs)

129. EFFECT OF LIPOSOME-ENCAPSULATED QUERCETIN ON DNA SYNTHESIS, LACTATE PRODUCTION, AND CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE LEVEL IN EHRLICH ASCITES TUMOR CELLS.

Podhajcer OL, Friedlander M, Graziani Y
Dept. Biology, Ben-Gurion Univ. Negev, Beer Sheva, Israel
Cancer Res; 40(4):1344-1350 1980

Quercetin (3,3',4',5,7-pentahydroxyflavone) entrapped within phospholipid vesicles inhibited (3H)thymidine incorporation and lactate production in Ehrlich ascites tumor cells. The presence of serum proteins in concentrations of up to 10 mg/ml did not alter the extent of the inhibitory effect of the liposome-entrapped flavone. At the same concentrations, serum proteins eliminated almost completely the inhibitory effects of the free quercetin on these metabolic processes. Prolonged sonication and different lipid compositions of the liposomes did not increase the inhibition of (3H)thymidine incorporation by the entrapped quercetin in the presence of serum albumin. On the other hand, serum albumin eliminated the elevation of the cyclic adenosine 3':5'-monophosphate level in these cells produced by both free and liposome-entrapped flavone. Attachment between Ehrlich ascites tumor cells and quercetin-loaded liposomes is demonstrated in negatively stained electron micrographs. The liposomes ranged in size from 50 to 100 nanometer. After 10 min of incubation, these liposomes were distributed randomly on the cell surface at distances of 100 to 200 nanometer. (Author abstract) (34 Refs)

130. EFFECT OF QUERCETIN ENTRAPPED IN PHOSPHOLIPID VESICLES ON EHRLICH'S ASCITES TUMOR CELL METABOLISM (MEETING ABSTRACT).

Podhajcer O, Graziani Y
Ben-Gurion Univ. Negev, Beersheba, Israel
Isr J Med Sci; 15(1):70 1979

In earlier in vitro studies, it was demonstrated that quercetin, a pentahydroxyflavone, at concentrations of 5 x 10(-5) M inhibits cell growth. Serum albumin (1-5 mg/ml) abolishes the inhibitory effect of this compound. To improve the availability of the bioflavonoid to cells in the presence of serum albumin, quercetin was entrapped into phospholipid vesicles (molar lipid ratio: 4/3/1, phosphatidylcholine/cholesterol/diacetylphosphate) and tested on [3H]thymidine incorporation, lactate production and cyclic AMP (cAMP) level. Our results indicate that both lactate formation and [3H]thymidine incorporation in Ehrlich's ascites tumor cells are inhibited by quercetin-loaded vesicles. The presence of 1.5 mg/ml serum albumin did not alter this inhibitory effect. Surprisingly, the increased level of cAMP induced by quercetin-loaded vesicles was abolished by the presence of the same concentration of serum albumin. Thus, the increased cAMP level effected by quercetin loaded vesicles is associated with the bioflavonoid effect on the exterior side of the cells. These data justify the use of quercetin-loaded vesicles for in vivo experimental studies. (no Refs)

131. INTRACELLULAR PENETRATION OF LIPOSOMES CONTAINING A WATER INSOLUBLE ANTIMITOTIC DRUG IN L1210 CELLS.

Fruhling J, Penasse W, Laurent G, Brassinne C, Hildebrand J, Vanhaelen M, Vanhaelen-Fastre R, Deleers M, Ruysschaert JM
Laboratoire des Radio-Isotopes, Service de Radiotherapie, Institut Jules Bordet, 1, rue Heger-Bordet, 1000 Bruxelles, Belgium
Eur J Cancer; 16(11):1409-1416 1980

To demonstrate the possibility of cell delivery of water insoluble products, L1210 cells were incubated with lipo-

somes containing Nocodazole (NCL), an experimental drug totally insoluble in water. Liposomes of various lipid compositions readily incorporated NCL, but only those formed from dipalmitoyl phosphatidylcholine, cholesterol and stearylamine (M ratio 4:3:1) had a clear affinity for L1210 cells, as shown by fluorescence studies. This affinity is mediated by the degree of both cell and liposome membrane fluidity. Cytoplasmic and intranuclear location of these liposomes containing NCL or drug-free and subcellular changes induced by their presence were demonstrated by ultrastructural studies. (Author abstract) (12 Refs)

132. ENHANCEMENT OF CYTOTOXIC ACTIVITY OF THALICARPINE BY ITS INCORPORATION INTO LIPOSOMES.

Todorov D, Delikonstantinos G
Res. Inst. Oncology, Sofia, Bulgaria
Onkologiia; 17(1):40-43 1980

The cytotoxic activity of alkaloid thalicarpine (TC) incorporated into negatively charged liposomes was tested in the cultures of Walker carcinosarcoma cells and lymphoma TLX5 cells. The cytotoxic activity, measured by the value of median inhibitory dose (ID50) of incorporated TC was significantly greater than that of free TC: 1.5 ug/ml and 5 ug/ml, respectively, in sensitive cells of Walker carcinosarcoma; 12 ug/ml and 31 ug/ml, respectively, in cells of Walker carcinosarcoma resistant to TC; and 0.3 ug/ml and 0.8 ug/ml, respectively, in TLX5 lymphoma. (10 Refs)

133. RAPID INDUCTION OF AMPHOTERICIN B SENSITIVITY IN L1210 LEUKAEMIA CELLS BY LIPOSOMES CONTAINING ERGOSTEROL (LETTER TO EDITOR).

Schiffman FJ, Klein I
Lab. Medicinal Chemistry and Biology, NCI, Bethesda, MD 20014
Nature (Lond); 269(5623):65-66 1977

L1210 leukemia cell cultures, incubated for 1 hr with egg yolk lecithin (EYL) liposomes containing ergosterol (0.05 mg/ml), then exposed for 2 hr to amphotericin B (2-8 ug/ml), showed cellular lysis at the end of treatment. Growth inhibition and/or a continuing decline of cell number were noted 45 hr later. The cells were unable to exclude trypan blue. These effects were dose-dependent over an amphotericin concentration of 2-8 ug/ml. Treatment with buffer or ergosterol-free EYL liposomes did not confer amphotericin sensitivity. Incubation with EYL liposomes (with or without ergosterol) in the absence of amphotericin did not affect survival or membrane properties of the cells. It is suggested that the addition of ergosterol to the cell membranes conferred amphotericin sensitivity. (19 Refs)

134. EVALUATION OF LIPOSOMES AS CARRIERS OF ESTRACYT INTO TUMOR CELLS IN VITRO.

Freiburg JA
Univ. Notre Dame, Notre Dame, IN
Diss Abstr Int [B]; 38(11):5267-5268 1978

Liposomes were used in this study to evaluate their potential use as carriers for the clinically used antiprostatic drug, Estracyt. A cell line developed from a rat prostate adenocarcinoma was used to demonstrate in vitro uptake of Estracyt and enhancement of uptake using liposomes. Estracyt was shown to associate with positive, negative, and neutral liposomes. The degree and limit of association depended on the charge of the liposomes. Positive liposomes showed the greatest degree of association, but there was no limit to the amount of Estracyt that could be associated with these liposomes. Negative and neutral liposomes, however, showed a lesser degree of association, and a limit to the amount of Estracyt that could be associated with them. Dialysis of positive, negative, and neutral liposomes made with Estracyt showed that positive liposomes were less permeable to the drug than were negative and neutral liposomes. At the end of the dialysis period, liposome associated Estracyt was still detectable in the liposome suspensions. Cellular uptake of Estracyt was demonstrated to be very low. Two types of liposomes showed ability to enhance the uptake of Estracyt. Liposome-associated-Estracyt toxicity to cells in vitro, however, was not enhanced over that of the free drug. It was concluded that although association of liposomes with Estracyt could be determined and enhancement of uptake into cells in vitro demonstrated, the mechanism of uptake of the liposomes, probably endocytosis and fusion, placed most of the Estracyt into the lysosomes where the drug could not get to its target site in the cell - the DNA. The preferred mechanism of uptake would be by fusion of the entire liposome with the plasma membrane of the cell. Since the prostate tumor cells were responsive to Estracyt and liposomes in vitro, but not to Estracyt in vivo, there is a potential use for liposome-associated Estracyt in vivo.

B.

In vitro studies with liposome-encapsulated nucleic acids

135. EVIDENCE FOR TRANSLATION OF RABBIT GLOBIN MRNA AFTER LIPOSOME-MEDIATED INSERTION INTO A HUMAN CELL LINE.

Ostro MJ, Giacomoni D, Lavelle D, Paxton W, Dray S
Dept. Microbiology and Immunology, Univ. Illinois Medical Center, Chicago, IL, 60612
Nature (Lond); 274(5674):921-923 1978

Evidence is presented which indicates that cultures of human epithelial carcinoma cells (HEp-2) treated with liposomally encapsulated rabbit globin messenger (m)RNA are stimulated to produce a globin-like protein. Globin mRNA was isolated from the reticulocytes of rabbits suffering from phenylhydrazine-induced anemia and sequestered within liposomes. HEp-2 cells were mixed with the liposomes in the presence of 3H-amino acids with or without transcription inhibitors (actinomycin D or alpha-amanitin). The cells were lysed and the soluble proteins were examined by electrophoresis on sodium dodecyl suflate polyacrylamide gel and by sucrose gradients. Electrophoresis showed that all liposome-treated preparations had three major peaks of radioactivity with relative fronts (Rf) of 0.30, 0.50, and 0.75. The 0.75 value corresponded to the Rf of the rabbit globin standard and was found only in liposome-treated cells. Actinomycin D enhanced this peak. Sucrose gradient profiles showed that although other proteins appear, isolates obtained from cells treated with liposomally sequestered mRNA exhibit a peak of radioactivity co-sedimenting with the globin subunit standard. This peak was absent in control cell lysates. With the addition of purified monospecific antibody to the cell protein isolates, the radioactive peak corresponding to the globin subunit standard shifted to the bottom of the gradient. This shift was inhibited by the addition of excess nonradioactive globin before the addition of antibody. The results show that HEp-2 cells, treated with liposomally encapsulated globin mRNA, were stimulated to synthesize a previously nonexistent globin-like protein product which reacts with monospecific goat anti-rabbit globin antibody. (24 Refs)

136. LIPOSOME ENTRAPPED RNA TRANSFERS SENSITIVITY TO PERITONEAL EXUDATE CELLS FOR A CHEMICALLY DEFINED ANTIGEN (ARSNAT) (MEETING ABSTRACT).

Paque RE, Magee WE, Nealon T
Dept. Microbiology, Univ. Texas Health Science Center, San Antonio, TX, 78284
Fed Proc; 38(3,part2):1093 1979

Liposomes have been utilized for protective transport of biologically labile materials in a number of mammalian systems. Our study assesses whether lymphoid cell RNA entrapped in liposomes can transfer cellular reactivity for a chemically defined antigen to guinea pig peritoneal exudate cells (GP-PEC). RNA was extracted from the spleens or lymph nodes of strain 2 guinea pigs skin test sensitive to mono(p-azobenzene-arsonate)-N-chloroacetyl-L-tyrosine (ARSNAT). The RNA with anti-guinea pig lymphocyte antibody was incorporated into positively-charged multilamellar liposomes. These target-directed liposomes were incubated for 15 min with 2 x 10(7) 'nonsensitive' GP-PEC. Transfer of sensitivity to the GP-PEC cells was tested in the presence of specific and nonspecific antigens in the agarose-droplet cell-migration-inhibition assay. In five experiments, GP-PEC incubated with liposomes containing anti-ARSNAT RNA transferred ARSNAT sensitivity; mean migration indices ranged from 35 +-4 to 56 +-3. GP-PEC incubated with liposomes alone, keyhole limpet hemocyanin (KLH), or coccidioidin failed to transfer ARSNAT sensitivity to GP-PEC. Protection of lymphoid cell immune RNA by entrapment within liposomes may offer an approach for in vivo transfer of cellular sensitivity by protection of immunobiologically active RNA. (no Refs)

137. CELLULAR UPTAKE AND PROTECTION AGAINST VIRUS INFECTION BY POLYINOSINIC-POLYCYTIDYLIC ACID ENTRAPPED WITHIN PHOSPHOLIPID VESICLES.

Mayhew E, Papahadjopoulos D, O'Malley JA, Carter WA, Vail WJ
Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263
Mol Pharmacol; 13:488-495 1977

138. LIPID VESICLES AS VEHICLES FOR THE INTRODUCTION OF VIRUS AND NUCLEIC ACIDS INTO CELLS.

Wilson AT, Tazewell A
State Univ. New York, Buffalo, NY
Diss Abstr Int [B]; 39(9):4201 1979

Large vesicles composed of phosphatidylserine are capable of encapsulating whole poliovirus and poliovirus RNA and delivering the encapsulated material to cells in an infectious form. Encapsulated virus is resistant to neutralizing antibody and can infect cells that lack the surface receptor required for the normal pathway of infection. Encapsulated RNA is resistant to ribonuclease and highly infectious. Quantitative measurements of cell-vesicle interactions in this system indicate that about 10% of the applied vesicles become stably associated with cells but about 90% of the entrapped material is released from the vesicles under these conditions. Approx 0.5% of the cell-associated RNA forms an infection in the cells, a number comparable to the specific infectivity of whole virus under similar conditions. Treatment of vesicle preparations with ribonuclease was found to increase the level of vesicle-mediated delivery by a factor of 10-50. (Author abstract) (no Refs)

139. INTRODUCTION OF LIPOSOME-ENCAPSULATED SV40 DNA INTO CELLS.

Fraley R, Subramani S, Berg P, Papahadjopoulos D
(c/o Papahadjopoulos) Cancer Res. Inst., Sch. Medicine, Univ. California, San Francisco, CA, 94143
J Biol Chem; 255(21):10431-10435 1980

DNA, isolated from Simian virus 40 (SV40), has been encapsulated in large (0.4-um diameter) unilamellar phospholipid vesicles. The procedure used for liposome preparation encapsulated the SV40 DNA at high efficiency (30 to 50% entrapment) and did not alter the physical or biological properties of the DNA molecules. The biological activity of the liposome-entrapped viral DNA was determined by plaque assays on a permissive monkey cell line. The infectivity of liposome-entrapped SV40 DNA was enhanced at least 100-fold over that of free naked DNA. Importantly, the infectivity of vesicle-entrapped DNA was resistant to DNase digestion, dependent on the amount of DNA encapsulated per vesicle and on the vesicle lipid composition. Liposomes composed of phosphatidylserine were the most efficient for delivery of DNA to cells (1.8 x 10(3) plaque-forming units/ug of DNA). Following the incubation of DNA-containing liposomes with cells, their infectivity could be enhanced an additional 10-to 200-fold by exposing the cells to high concentrations of polyethylene glycol or glycerol. Under these conditions the infectivity of liposome-encapsulated SV40 DNA (3 x 10(5) plaque-forming units/ug) was comparable with values reported using the calcium phosphate method. In addition to providing a sensitive assay for monitoring and optimizing the delivery of vesicle contents to cells, the liposome-mediated delivery of nucleic acids may have potential for increasing the efficiency of DNA delivery to cells and for extending the number of cell types which can be transformed or transfected. (Author abstract) (36 Refs)

140. THE INTRODUCTION OF POLIOVIRUS RNA INTO CELLS VIA LIPID VESICLES (LIPOSOMES).

Wilson T, Papahadjopoulos D, Taber R
Dept. Viral Oncology, Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cell (Camb); 17(1):77-84 1979

Large unilamellar vesicles (LUV) composed of phosphatidylserine are capable of encapsulating poliovirus RNA and delivering it efficiently to cells in an infectious form. The biological activity of vesicle-entrapped poliovirus RNA was 1-2 x 10(4) plaque forming units (pfu)/nanog (ng) and appeared to be enhanced by ribonuclease treatment of the vesicle preparations (infectivity = 1-2 x 10(5) pfu/ng). Vesicle-mediated RNA infection produced equivalent titers in primate and nonprimate cells. Moreover, the data strongly suggest that the ratio of molecules per infectious unit is close to one when the RNA is properly delivered to the cell. A comparative study of LUV and multilamellar vesicles (MLV) indicates that LUV deliver their contents to the cell cytoplasm much more efficiently than MLV. LUV-entrapped poliovirus RNA produced infectious titers 10-100 fold higher than comparable RNA preparations delivered to cells by other techniques. (Author abstract) (28 Refs)

141. ATTEMPTS AT HIGH FREQUENCY TRANSFORMATION OF PLANT CELLS (MEETING ABSTRACT).

Dellaporta SL, Giles KL
Iowa State Univ., Ames, IA, 50010
In Vitro; 15(3):190 1979

Studies on the high frequency transformation of plant cells in culture by Agrobacterium tumefaciens are under way.

Whole bacterial cells can be taken up by plant protoplasts, and bacterial L-forms fused with plant protoplasts under the influence of polyethylene glycol treatment. Auxin and cytokinin auxotrophy was used for the detection of transformation and octopine synthesis monitored. We are also investigating plant cell transformation using plasmid DNA isolated from A tumefaciens. Plant cell protoplasts are incubated with the plasmid DNA and then screened for habituation as before. *Liposomes* containing plasmid DNA can also be fused with protoplasts and the effectiveness of these bodies in duplicating crown gall characteristics will be discussed. (no Refs)

C.

In vitro studies with other substances encapsulated in liposomes

142. INDUCTION OF TYROSINE AMINOTRANSFERASE IN H-35 HEPATOMA CELLS BY CAMP CAPTURED IN PHOSPHOLIPID VESICLES.

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J Cell Biol; 88(1):89-95 1981

The uptake, metabolism, and action of cAMP, captured within phospholipid vesicles, in H-35 hepatoma cells were studied. Sonication of lipids in buffer containing cAMP resulted in the formation of 300-A unilamellar lipid vesicles, capturing cAMP in the internal aqueous cavity. Incubation of H-35 hepatoma cells with vesicles containing cAMP (vesicle-cAMP) resulted in rapid incorporation of the vesicle content; apparent saturation of uptake was reached after approx 30 min of incubation at 37 C. Uptake of vesicle-cAMP was linear over a 10-fold vesicle concentration range. Pretreatment of cells with combined inhibitors of glycolysis and respiration inhibited vesicle uptake by 27%, suggesting vesicle fusion with the cell membrane as a predominant pathway of vesicle uptake. Studies on the metabolism of incorporated cAMP indicated that greater than 50% of the cell-associated radioactivity, derived from vesicle-[3H]cAMP, was preserved as cAMP at the end of a 20-min incubation at 37 C. The incorporation of vesicle-cAMP by H-35 hepatoma cells resulted in increased tyrosine aminotransferase (TAT) activity. The concentration of vesicle-cAMP needed to produce a half-max increase in TAT activity was 10 uM, approx two orders of magnitude lower than that of exogenously added dbcAMP. cAMP was ineffective when added extracellularly. The kinetic relationship of the cAMP-induced increase in TAT activity and the binding of cAMP to its receptor protein, in intact H-35 cells, was examined using vesicle-trapped 8-N3-cAMP, a photoaffinity labeling analogue of cAMP. Incubation of H-35 hepatoma cells with vesicle-8-N3-cAMP resulted in increased TAT activity, preceded by the binding of 8-N3-cAMP to the regulatory subunit of Type II cAMP-dependent protein kinase. The use of lipid vesicles provides a means of modulating intracellular cAMP concentration without adding cyclic nucleotide in the millimolar concentration range to the extracellular medium. The increased efficiency of intracellular delivery of cyclic nucleotide with retention of biological activity, provides a useful technique in examining the relationship of occupancy of specific cAMP-receptor protein(s) and the occurrence of a cAMP-mediated biological response in intact cells. (Author abstract) (33 Refs)

143. NEOPLASTIC TRANSFORMATION, SOMATIC MUTATION, AND DIFFERENTIATION.

Ts'o PO

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Carcinogenesis: Fundamental Mechanisms and Environmental Effects, Proceedings of the Thirteenth Jerusalem Symposium on Quantum Chemistry and Biochemistry held in Jerusalem, 28 April - 2 May, 1980. Vol. 13, Pullman B, Ts'o PO, and Gelboin H, ed.Boston, D. Reidel Publishing Company, The Jerusalem Symposia on Quantum Chemistry and Biochemistry, 592 pp., 1980.

The use of the Syrian hamster embryonic (SHE) cell system to study neoplastic transformation, somatic mutations, and differentiation is described. In SHE cells, it can be shown that cloning efficiency in semisolid agar, which is a property of anchorage-independent growth, is highly correlated with tumorigenicity, with a statistical confidence level of 99%. It also appears that enhancement of fibrinolytic activity and growth in 1% serum also are closely related to tumorigenicity, with a confidence level of 95%. Through the use of the SHE system it has been possible to show that neoplastic transformation in vitro is a progressive process going through qualitatively different stages: alteration in clonal morphology (2 wk), enhancement in fibrinolytic activity (2-4 wk), growth on confluent cell mat (4-8 wk), growth in low serum (4-12 wk), growth in low calcium (4-12 wk), and growth in soft agar or agarose (8-16 wk). Thus, an analogy can be drawn to the progressive nature of in vivo and in vitro carcinogenesis. With SHE cells, it has been possible to show that specific perturbation to DNA alone, by treatment with bromodeoxyuridine and near-UV light, incorporation of methy [3H]-thymidine, or treatment with *liposomes containing deoxyribonuclease I*, is sufficient to initiate neoplastic transformation. With this SHE cell system, it is now possible to make a quantitative evaluation of the relationship between somatic mutation and neoplastic transformation. The clonal isolation of cells from this system at the different stages during the process of progression has allowed the study of the progression and stability of these variant clones upon further growth or upon second mutagenic perturbation. The use of SHE cells as a model for the study of cellular differentiation is discussed. (15 Refs)

144. CELL KILLING AND SOMATIC MUTATION OF MAMMALIAN CELLS IN CULTURE INDUCED BY SPECIFIC NUCLEASES ENCAPSULATED IN LIPOSOMES (MEETING ABSTRACT).

Zajac M, Hershner SE, Ts'o PO

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J Cell Biol; 83(2,part2):442a 1979

To study somatic mutation and neoplastic transformation in mammalian cells, we have used negatively charged phosphatidylserine large unilamellar vesicles to deliver active nucleases inside the cell, thus providing a direct and specific perturbation to the genetic apparatus. Upon fusion of liposomes with the plasma membrane, the encapsulated enzymes are released into the cytoplasm. Transformed Syrian hamster cells previously used for somatic mutation studies in our laboratory were treated for 2.5 hr at 37 C with empty liposomes, exogenous DNase I, pancreatic RNase and the above nucleases separately entrapped in liposomes. Cell survival, measured by growth and cloning efficiency assayed immediately after removal of liposomes, was not affected by treatment with empty liposomes (12 mg) or exogenously added nucleases (7 mg DNase I; 7-1,000 mg RNase). In con-

trast, the survival curve of cells treated with constant amounts of liposomes (12 mg) containing varying amounts of DNase I (1-8 mg not corrected for the efficiency of the entrapment) showed a 10-35% linear reduction up to 4 mg of DNase I and the sharp decline at higher amounts of enzymes (approx 3% survival with 5.5 mg DNase I). Similarly, cells treated with RNase-in-liposomes (7 mg RNase used for entrapment into 8.5 mg lipids) showed 20% survival. Somatic mutation at the hypoxanthine guanine phosphoribosyl transferase locus of cells treated with DNase-in-liposomes, exogenous DNase I and empty liposomes were measured after 14 days in culture. Preliminary results indicate that the mutation frequency of cells treated with DNase-in-liposomes is approx 10(-5)/surviving cells representing 3-to 6-fold above the frequency observed in control cells. The dose response curve shows the highest mutation frequency occurring at lower doses of enzyme. These results suggest a novel approach for the direct and specific perturbation of the genetic apparatus in living mammalian cells by enzymes encapsulated in liposomes. (1 Ref)

145. NEOPLASTIC TRANSFORMATION INDUCED BY DNASE I ENCAPSULATED IN LIPOSOMES (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 21:127 1980

To study somatic mutation and neoplastic transformation (NT) in diploid Syrian hamster embryo (SHE) cells, we have used phosphotidylserine liposomes to deliver active deoxyribonuclease I (DNase I) inside the cell, thus providing a direct and specific perturbation to the genetic apparatus. We showed: the entrance of DNase I inside the cell by the dose-dependent cytotoxicity of this treatment, and 2) the entrance of DNase I into nucleus by the induction of somatic mutation at the HGPRT locus. For NT studies, SHE cells were treated with 0.5 mg of DNase I in 1 mg liposomes (D-L) or 1 mg of empty liposomes for 2.5 hr at 37 C. During the 4 mo in culture, cells were split at confluency by seeding 10(6) cells/75 cm2 flask. Within 5 wk, their growth rate declined and cultures entered crisis. Three out of four control cultures (C) senesced. The treated cultures (D-L) and one C culture recovered and grew vigorously. Both D-L and C lines showed increased cloning efficiency (25-40%) in liquid media (200 to 500 cells/100 mm dish, 0% for normal SHE cell). However, only the D-L cultures can grow in 1% serum medium (2.8% CE, 10(4) cells/100 mm dish) and in 0.3% agar (0.25% CE, 10(5) cells/60 mm dish). In addition, the D-L culture at passage (P) 36 (population doubling (PD) = 63) was tumorigenic in 9/9 newborn hamsters (2 x 10(6) cells sc injection, 3 wk latent period), while the C culture was not tumorigenic at P38 (PD = 85). This novel approach indicates that damage to DNA alone can initiate NT process supporting the earlier conclusion based on BrdU+UV irradiation experiments from our laboratory. However, specific DNA damage is not sufficient for NT since long progression process is required after the initial insult. This finding also implicates the possibility of initiation of NT due to insults causing the release of internal nucleases. (2 Refs)

146. BENZO(A)PYRENE METABOLISM OF PURIFIED FORMS OF RABBIT LIVER MICROSOMAL P-450, CYTOCHROME B5 AND EPOXIDE HYDRASE IN RECONSTITUTED PHOSPHOLIPID VESICLES.

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Biochem Biophys Res Commun; 95(1):431-439 1980

The results of reconstitution studies of the metabolism of benzo(a)pyrene (BP) using purified forms of cytochrome P-450, cytochrome B5, and epoxide hydrase are reported. Enzymes were prepared from rabbit liver microsomes, and their purified forms were incorporated into phospholipid vesicles with the cholate gel technique. It was found that various forms of P-450 showed varying specificities toward BP. P-450LM2 efficiently converted BP to 4,5-dihydroxy-4,5-dihydro-benzo(a)pyrene in the presence of epoxide hydrase. P-450 LM4, however, preferentially metabolized BP to 9,10-dihydroxy-dihydrobenzopyrene. BP was not a substrate for P-450 LM3. Five-fold and 3-fold increases in activity of P-450 LM2 and P-450 LM4, respectively, occurred in the presence of cytochrome B5. LM2 is the phenobarbital-induced, LM4 the methylcholanthrene-induced, and LM3 the uninduced form of cytochrome P-450. (26 Refs)

147. MODIFICATION OF MITOCHONDRIAL DNA BY A DIHYDRODIOL-EPOXIDE DERIVATIVE OF BENZO(A)PYRENE (MEETING ABSTRACT).

Backer JM, Weinstein IB

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Proc Am Assoc Cancer Res; 21:93 1980

Previous studies have demonstrated that (+-)-7beta,8alpha-dihydroxy-9alpha,10alpha- epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BPDE) binds to nuclear DNA (nDNA) and induces mutations in nuclear genes in mammalian cells, but other possibly critical cellular targets have not been excluded. In this study, we have examined covalent binding of BPDE to mitochondrial DNA (mtDNA) in mouse embryo 10T1/2 cells, rat liver K16 cells, and mouse L cells. In all 3 cell cultures, the extent of modification (picomoles BPDE/nanomoles nucleotides) of mtDNA was 40-90 x greater than that of nDNA. On the other hand, purified mtDNA and nDNA were modified to equal extents when reacted in soln with BPDE. We also examined the intracellular distribution of DNA and BPDE in 10T1/2 cells exposed to BPDE for 20 min. The nuclear fraction contained 99% of total cellular DNA and 30% of cell-associated BPDE. The respective values for the mitochondrial fraction were 1% and 15%. The high BPDE content of mitochondria presumably reflects the lipophilicity of BPDE and the high membrane content of mitochondria. Studies with synthetic *liposome-DNA complexes* demonstrated that BPDE in a lipid phase readily reacts with DNA. Extensive modification of mtDNA was also seen in 10T1/2 cells exposed to the parent hydrocarbon benzo(a)pyrene. Thus, lipophilic carcinogens can concentrate in cellular mitochondria and preferentially react with mtDNA. MtDNA may, therefore, be a biologically significant target during chemical carcinogenesis. (no Refs)

148. THE ROLE OF MICROFILAMENTS IN THE RESPONSE OF ADRENAL TUMOR CELLS TO ADRENOCORTICOTROPIC HORMONE.
Hall PF, Charpponnier C, Nakamura M, Gabbiani G
Dept. Physiology, Univ. California, Irvine, CA, 92717
J Biol Chem; 254(18):9080-9084 1979

Highly purified anti-actin was prepared from sera of patients suffering from hepatitis by affinity chromatography using actin as ligand. The *anti-actin was entrapped within liposomes* prepared from phosphatidylcholine and phosphatidylserine and presented to Y-1 mouse adrenal tumor cells. Such liposomes were also prepared with entrapped cyclic [3H]AMP; this method of presenting the cyclic nucleotide to the cells lowered the threshold to cyclic AMP by 2 orders of magnitude compared to free nucleotide as judged by production of 20alpha-dihydroprogesterone. Y-1 cells were incubated with liposomes containing buffer or buffer with anti-actin for 1 hr. When the medium was changed and incubation was continued with 0.9% NaCl (saline), adrenocorticotropic hormone (ACTH), or dibutyryl cyclic AMP, it was found that incubation with anti-actin inhibited three steroidogenic responses to ACTH and dibutyryl cyclic AMP: (i) increased production of 20alpha-dihydroprogesterone; (ii) increased production of pregnenolone in isolated mitochondria prepared from cells previously incubated with either stimulating agent; (iii) increase in the cholesterol content of inner mitochondrial membranes isolated from cells incubated with aminoglutethimide (an inhibitor of side chain cleavage of cholesterol) and ACTH. Liposomes containing buffer were without detectable effect on the response to ACTH. Normal human IgG, boiled anti-actin, and anti-actin plus excess actin in liposomes were without effect on the subsequent response to ACTH. These findings, together with previous evidence, suggest that ACTH and cyclic AMP stimulate steroidogenesis by increasing the transport of cholesterol to the mitochondrial side chain cleavage enzyme by a mechanism involving actin. (Author abstract) (29 Refs)

149. ESTROGEN-INDUCED MEMBRANE ALTERATIONS AND GROWTH ASSOCIATED WITH PROTEINASE ACTIVITY IN ENDOMETRIAL CELLS.
Pietras RJ, Szego CM
Dept. Biology, Molecular Biology Inst., Los Angeles, CA, 90024
J Cell Biol; 81(3):649-663 1979

Endometrial cells isolated from uteri of ovariectomized rats were treated in vitro with 1 x 10(-9) M estradiol-17beta (E2B) to analyze early changes in membrane properties during hormone-induced growth. After 30-min exposure to E2B at 22 C, cells exhibited an enhanced capacity to bind RBC (hemadsorption) in the presence of concanavalin A (Con A) to 237% of the level in paired controls. Fluorescence microscopy revealed that approx 25% of cells exposed to E2B, but not estradiol-17alpha (E2A), showed a redistribution into polar clusters of Con A binding sites that were dispersed in random patches at the external surfaces of control cells. These hormone-induced membrane alterations were abolished by prior treatment of cells with inhibitors of thiol proteinase activity of the cathepsin B1 (CB1) type, such as leupeptin and iodoacetate. Leupeptin at 4.5 X 10(-7) M also reduced the affinity of 3H-E2B binding to intact cells but did not influence specific binding of the hormone to macromolecular components of cytosol. A pronounced increase in the availability of endogenous CB1, but not of alkaline phosphatase, succinate, or lactate dehydrogenase, in the extracellular media was elicited within 30 min after E2B treatment. In cells cultured in chemically defined medium for up to 48 hr, E2B but not E2A enhanced cell proliferation and stimulated 3H-thymidine incorporation into macromolecular form. These E2B induced effects were abolished by prior treatment of cells with *liposome-entrapped leupeptin* at a final concentration of 7 x 10(-8) M. The net rate of intercellular adhesion among endometrial cells was also enhanced by E2B. This hormonal response was diminished by prior exposure to leupeptin. Fractionation of cells by selection for adhesiveness due to E2B exposure for 30 min yielded a subpopulation of rapidly dividing cells which surpassed their less adhesive counterparts in cathepsin secretion and in Con A-mediated hemadsorption. These results indicate that leupeptin-sensitive proteinase activity may contribute to membrane and growth modifications elicited by E2B treatment in endometrial cells. (Author abstract) (62 Refs)

150. HERITABLE MEMBRANE ALTERATIONS AND GROWTH ASSOCIATED WITH ENHANCED LEUPEPTIN-SENSITIVE PROTEINASE ACTIVITY IN EPITHELIAL CELLS EXPOSED TO DIBUTYLNITROSAMINE IN VITRO.
Pietras RJ
Dept. Biology, Univ. California, Los Angeles, CA, 90024
Cancer Res; 38(4):1019-1030 1978

Early changes in male bullfrog (Rana catesbeiana) and male New Zealand white rabbit urinary bladder epithelium were examined following in vitro treatment with varying amounts of dibutylnitrosamine (DBN) and the noncarcinogen diphenylnitrosamine (DPN). At 5 chi 10-(4) M DBN, there were max increments in labeled thymidine incorporation and growth in cells maintained in serum-free, chemically defined medium, compared with control cells and cells treated with DPN. The DBN-induced effects were abolished by prior treatment of cells with *liposome-entrapped leupeptin* and were reduced by ovomucoid, but not by soybean trypsin inhibitor. Extracellular release of cathepsin B1 activity was enhanced to 280% of that of control cells within 1 hr of DBN treatment. Concanavalin A (Con A)-mediated binding of RBC, but not Con A binding to bullfrog cells increased to 194% of the level in cells treated for 1 hr with DPN. Furthermore, fluorescence microscopy indicated that 20% of the cells exposed to DBN showed a clustering of Con A-binding sites that are normally distributed at random on the external cell surface. Intercellular adhesion was also enhanced following DBN treatment. The DBN-induced membrane alterations were diminished by treatment with cathepsin B1 inhibitors and were propagated during 14-day culture after the initial DBN exposure. Fractionation of cells by selection for enhanced adhesiveness due to DBN exposure for 30 min elicited a rapidly dividing cell fraction active in cathepsin B1 secretion, compared with their less adhesive counterparts. Thus, the heritable membrane alterations and enhanced cell growth induced by DBN are associated with increases in the activity of a leupeptin-sensitive proteinase at the external cell surface. (59 Refs)

151. EFFECT OF INHIBITORS OF LYSOSOMAL CATHEPSIN ON PROTEIN DEGRADATION IN RAT HEPATOCYTES (MEETING ABSTRACT).
Suleiman SA, Jones GL, Singh H, Vestling CS
Dept. Biochemistry, Univ. Iowa, Iowa City, IA, 52242
Fed Proc; 38(3,part1):835 1979

The effect of leupeptin (inhibitor of cathepsin B) and pepstatin (inhibitor of cathepsin D) has been studied in primary cultures of hepatocytes isolated from adult rat livers by the collagenase perfusion technique. Hepatocytes were labeled with either 3H-leucine alone or 3H-leucine and 35S-methionine for 30 min. After pulse label, cells were washed and

resuspended in fresh Swim's medium. In 30 min, addition of leupeptin (33 uM) abolished cathepsin B activity, but *liposome packaged pepstatin* (30 ug/ml) resulted in 40% loss of cathepsin D activity. Leupeptin caused 70-90% reduction in degradation of 3H-leucine-labeled proteins while pepstatin or a combination of both inhibitors caused no more than 50% reduction in the degradation of 35S-methionine-labeled intracellular proteins and 40% increase in the release of 35S-methionine-labeled proteins into the suspending medium. Leupeptin caused much less effect on 35S-methionine labeled proteins. The specific activity of mitochondrial malate dehydrogenase is not affected by the addition of either inhibitor, but the specific activity of lactate dehydrogenase is increased 45% by addition of leupeptin. The results suggest that cathepsin B and D (and their specific inhibitors) play an important role in regulating the balance between biosynthesis and degradation of intracellular proteins. (no Refs)

152. MICROINJECTION OF RICIN ENTRAPPED IN UNILAMELLAR LIPOSOMES INTO A RICIN-RESISTANT MUTANT OF BABY HAMSTER KIDNEY CELLS.

Gardas A, Macpherson I
Dept. Biochemistry, Medical Center Postgraduate Education, Marymoncka 99, 01-813 Warszawa, Poland
Biochim Biophys Acta; 584(3):538-541 1979

Fluorescein-labeled Ricin was entrapped in unilamellar liposomes; 14 ug of protein was entrapped by 1 mg of lipids. Liposomes added to cells in culture in low serum medium can deliver entrapped Ricin to a Ricin-resistant mutant of baby hamster kidney (BHK) cells. Ricin entrapped in unilamellar liposomes inhibits protein biosynthesis at a concentration of 1.75 ug/ml in Ricin-resistant cells. Ricin dissolved in medium at 50 ug/ml does not affect protein synthesis in these cells. (Author abstract) (21 Refs)

153. LIPOSOME-MEDIATED RICIN TOXICITY IN RICIN-RESISTANT CELLS.

Dimitriadis GJ, Butters TD
Natl. Inst. Medical Res., Ridgeway, Mill Hill, London NW7 1AA, England
FEBS Lett; 98(1):33-36 1979

The preparation of liposomes containing ricin and their effect on protein synthesis after fusion with normal and ricin-resistant BHK cells are described. Preparation of liposomes included evaporation of a chloroform solution of phosphatidyl choline, phosphatidyl serine, and cholesterol (in molar rations 9:1:10) to dryness under vacuum. The lipid film was incubated with or without ricin (containing trace amounts of 125I-ricin), vortexed, sonicated, and purified by Sephadex chromatography. When empty liposomes were incubated with either BHK cells or RicR14 cells (a clone of BHK cells resistant in vivo to ricin toxicity), no effect on protein synthesis was observed. When liposomes containing ricin were incubated with either of these cells, incorporation of leucine was inhibited. Free ricin (same concentration as ricin entrapped in liposomes) added to RicR14 cells resulted in markedly less protein inhibition than that observed with ricin-containing liposomes, but the addition of free ricin to BHK cells inhibited protein synthesis to a greater extent than ricin-containing liposomes. The results show that ricin can inhibit protein synthesis in ricin-resistant RicR14 cells if a mechanism which introduces ricin into the cytoplasm is provided. (18 Refs)

154. MECHANISM OF RESISTANCE TO RICIN TOXIN IN SELECTED MOUSE LYMPHOMA CELL LINES.

Nicolson GL, Poste G
Dept. Developmental and Cell Biology, Univ. California, Irvine, CA, 92717
J Supramol Struct; 8(3):235-245 1978

A murine BW5147 lymphoma variant line, selected stepwise against a series of increasing ricin concentrations, was compared with the wild-type line for resistance to and uptake of low concentrations of ricin. 125I-Ricin was conjugated to ferritin and bound to cells. Ferritin-125I-ricin and ricin had equivalent effects on growth characteristics of parental or resistant lines when present continuously in the cell culture for 24-72 hr or when present for 10 min and removed. At low toxin concentrations, binding of ferritin-125I-ricin was similar to, but slightly lower than, that of 125I-ricin. No difference in the quantitative binding of the two labels to wild-type or resistant strain was observed during 10 min incubations. Wild-type cells showed marked inhibition of cell protein synthesis after an initial lag of 45-60 min when exposed to 10 min pulses of ricin or ferritin-125I-ricin. A higher toxin concentration reduced the lag slightly. Ultrastructural examination of fixed, ferritin-125I-ricin-pulsed cells showed approx equal numbers of ferritin-toxin molecules bound to either cell type in a dispersed distribution. The presence of lactose prevented binding of label to the cells. Endocytosis was observed in wild-type cells pulsed for 10 min, incubated at 37 C for 60 min, and then fixed. No internalization was observed in the resistant line. At high concentrations of toxin, endocytosis was observed in both lines. Incubation of wild-type cells in medium containing *encapsulated ricin* produced rapid inhibition of cellular protein synthesis which was significantly faster than the inhibition observed in such cells in the presence of free toxin, a combination of empty lipid vesicles together with free toxin or empty vesicles alone. Rapid inhibition was only observed in resistant cells containing encapsulated toxin. (37 Refs)

155. RESPONSE OF NORMAL AND NEOPLASTIC MAMMARY CELLS TO PHOSPHOLIPID VESICLES CONTAINING UNESTERIFIED OLEIC ACID.

Hosick HL
Dept. Zoology, Washington State Univ., Pullman, WA, 99164
Cell Mol Biol; 24(4):363-368 1979

Reactions of mammary epithelial cells to unesterified oleic acid have been analyzed. In order to directly and efficiently insert oleic acid into monolayers of mammary cells, the unesterified oleic acid was first co-dispersed with phospholipids in Ca-Mg-free saline and then sonicated. The fatty acid became incorporated into the resulting phospholipid vesicles ('liposomes'). Cells from mid-pregnant mammary gland of mouse, or from mammary tumors, maintained in primary monolayer culture, were then incubated with such phospholipid vesicles. The uptake of vesicles by both normal and tumor cells was sensitive to the composition of the medium in which vesicles were supplied to cells, and to the concentration of vesicles in the medium. The composition of such 'liposomes' was important in determining their rate of uptake, and significant differences were noted in uptake by normal vs tumor cells. The liposome-associated unesterified oleic acid supplied to normal mammary cells was rapidly incorporated into compounds, especially triglycerides and phospholipids. In neoplastic mammary cells, a smaller proportion was incorporated into phospholipid and more into other lipid classes. Growth of cells was also measured after treatment. Growth was defined as accumulation of DNA during a 3-day post-treatment incubation period with

medium containing 10% fetal calf serum and 5 ug/ml insulin. Serum lipids affected the growth response to liposomes. Amount of DNA in control culture (mock-treated) decreased about 30% when lipid-free serum was used instead of intact serum in the culture medium, indicating the cells do respond somewhat to serum lipids. This depression of growth was not overcome when cells were treated with liposomes in the lipid-free medium. This survey suggests that monolayer cultures and liposomes can be successfully used to probe in more detail the growth responses of mammary epithelial cells to fatty acid, and suggests also how this responsiveness changes during progression to neoplasia. (Author abstract) (20 Refs)

156. UPTAKE AND UTILIZATION OF FREE FATTY ACIDS SUPPLIED BY LIPOSOMES TO MAMMARY TUMOR CELLS IN CULTURE.

Hosick HL
Dept. Zoology, Washington State Univ., Pullman, WA, 99164
Exp Cell Res; 122(1):127-136 1979

Cells from C3H mouse mammary adenocarcinomas maintained in primary monolayer culture were incubated with phospholipid-oleic acid vesicles, and optimal conditions for uptake were established. When phosphatidyl choline and phosphatidyl serine were used to make the vesicles, the oleic acid was taken up more efficiently than when it was complexed to albumin. The oleic acid taken up by the cells was rapidly incorporated into cellular triglycerides and phospholipids. By 3 days after the cultures were treated, their DNA contents, measured by fluorescence after reaction with diaminobenzoic acid, were 50% greater than those of control cultures. The magnitude of the growth response reflected liposome dosage and cell density. It was concluded that liposomes can be used to insert materials directly into epithelial cells by way of their apical surfaces and that substances thus introduced can be utilized metabolically by the cells. (37 Refs)

157. STIMULATION OF MAMMARY EPITHELIAL GROWTH BY FREE FATTY ACIDS AND CHANGES IN THIS RESPONSE DURING NEOPLASTIC PROGRESSION (MEETING ABSTRACT).

Hosick HL, Angello JC, Anderson ME
Dept. Zoology, Washington State Univ., Pullman, WA, 99164
Proc Am Assoc Cancer Res; 19:178 1978

Our purpose has been to analyze the role of exogenously-supplied fatty acids in governing the rate of proliferation of normal, preneoplastic, and neoplastic mammary epithelial cells. This purpose was suggested by the fact that normal mammary epithelium will proliferate only if surrounded by adipose tissue, which probably supplies it with free fatty acids, whereas cells from mammary adenocarcinomas seem to be considerably less fastidious in their lipid needs. To analyze cell responses more precisely, we use primary monolayer cultures of epithelial cells from three sources: midpregnant mammary gland, outgrowths of hyperplastic alveolar nodules, and spontaneous mammary adenocarcinomas of BALB/c and C3H mice. All three cell types attached and grew poorly (as assayed by DNA accumulation) in medium containing delipidated serum. Large amounts of fatty acids, especially oleate or linoleate, can be force-fed into these cells using *liposomes* as carriers. Growth of normal epithelial cells responds more strongly to such lipid supplements than does growth of tumor cells. However, cells replicate only if insulin and hydrocortisone are also present in the culture fluid. The exogenously supplied fatty acids are rapidly metabolized to phospholipids and triglycerides by both normal and neoplastic cells, but quantitative patterns of metabolism are distinctly different in the two. Other growth supplements (eg, extracts of mesenchyme) which we have shown to be effective in promoting proliferation of the cells also lose their potency if delipidated. We conclude that lipid composition of the extracellular milieu is an important factor in morphogenetic proliferation of mouse mammary epithelium, and that tumor cells have an altered sensitivity to this regulatory signal.

158. LIPIDS AS REGULATORS OF GROWTH AND OTHER PROPERTIES OF MOUSE MAMMARY CELLS IN MONOLAYER CULTURE (MEETING ABSTRACT).

Hosick HL
Washington State Univ., Pullman, WA, 99163
NCI Intercom; 7(4):9-10 1978

Mammary parenchyma of the mouse apparently responds during pregnancy to growth-promoting substances in adjacent white adipose tissue (the mammary fat pad). Preneoplastic parenchyma (hyperplastic alveolar nodules) proliferates in nonpregnant mice, but again only in white adipose tissue. Adenocarcinomas grow beyond the mammary fat pad. Adipose cells may liberate free fatty acids (FA) utilized locally during pregnancy by normal parenchyma to support growth. In this study, primary monolayer cultures of epithelioid cells from midpregnant mouse mammary gland, from outgrowths of hyperplastic alveolar nodules (D1 and D2) and spontaneous mammary adenocarcinomas from BALB/c and C3H mice were used to test the possibility that isolated mammary epithelial cells respond differently to FA depending on culture conditions and cell status with respect to neoplasia. *Vesicles* made of phosphatidylcholine and phosphatidylserine (9:1) effectively retain free FA and fuse with mammary cells. After a 2-hr pulse with the proper dosage of such liposomes carrying free oleic acid, growth of normal cells increases about two-fold over a 3 day period. The free FA is rapidly esterified and soon appears mostly in phospholipids and triglycerides. Qualitatively, metabolism is similar in normal and tumor cells, but marked quantitative differences are noted. Lipid composition of the culture medium also influences the adhesive properties of mammary cells. Culture medium containing delipidated serum does not promote efficient attachment of cells from midpregnant mice to the culture plate surface. The cells are capable of attachment when switched to medium containing whole serum. Neither a FA nor hydrocortisone when added to delipidated serum increases attachment rate of cells from midpregnant mice.

159. STIMULATION OF DNA SYNTHESIS BY AN ADENOVIRUS TYPE 12 T ANTIGEN FRACTION CONTAINING PROTEIN KINASE ACTIVITY AND ENCAPSULATED IN LIPOSOMES.

Allebach ES, Mannino RJ, Strohl WA, Raska K
Dept. Microbiology, Coll. Medicine and Dentistry New Jersey, Rutgers Medical Sch., Piscataway, NJ, 08854
Virology; 107(1):240-249 1980

Adenovirus type 12 T antigen extracted from transformed BHK21 cells (line T637) binds to double-stranded DNA (ds-DNA) and is eluted from a ds-DNA cellulose column in two fractions, at pH 6.2 and pH 8.0. The fraction eluting at pH 8.0, when encapsulated in large unilamellar phosphatidylserine vesicles, stimulates DNA synthesis in BHK21 cells arrested in the G1 phase of the cell cycle by serum deprivation. Unencapsulated material has no stimulatory effect. The pH 8.0 fraction also contains protein kinase activity which is immunoprecipitated by antisera reactive with T antigen. The fraction eluting at pH 6.2 contains no detectable pro-

tein kinase activity and, whether encapsulated or unencapsulated, does not stimulate DNA synthesis in growth-arrested BHK21 cells. (Author abstract) (35 Refs)

VI. HUMAN AND ANIMAL INVESTIGATIONS OF LIPOSOMES AS CARRIERS OF DRUGS AND OTHER SUBSTANCES

A.

Pharmacokinetics of liposome-encapsulated antitumor agents

160. TISSUE AND HEPATIC SUBCELLULAR DISTRIBUTION OF LIPOSOMES CONTAINING BLEOMYCIN AFTER INTRAVENOUS ADMINISTRATION TO PATIENTS WITH NEOPLASMS.

Segal AW, Gregoriadis G, Lavender JP, Tarin D, Peters TJ
Dept. Medicine, Royal Postgraduate Medical Sch., DuCane Rd, London, W12 OHS, England
Clin Sci Mol Med; 51(4):421-425 1976

The subcellular distribution of liposomes containing In-labeled bleomycin was studied following iv administration to a 73-yr-old man (patient 1) with hepatic metastases from a pancreatic adenocarcinoma and to a 69-yr-old man (patient 2) with hepatocellular carcinoma in a cirrhotic liver. Technetium-labeled colloid liver scans and scans after injection of the labeled bleomycin showed defects in the uptake representing tumor deposits. At 27 hr after liposome injection in patient 1, much of the radioactivity was in the bone marrow, although there was considerable hepatic radioactivity. In patient 2, even at 90 min after liposome injection, there was a considerable amount of bone marrow radioactivity. The distribution of radioactivity in a percutaneous liver biopsy homogenate indicated that activity almost exactly paralleled that of the lysosomal marker enzyme N-acetyl-b-glucosaminidase. When liposomes containing bleomycin were added to the homogenate from a normal control in vitro, radioactivity remained largely in the sample layer, and only trace amounts were associated with the various organelles, including the liposomes. Both patients died from gastrointestinal hemorrhage of unknown cause 8 days after injection with liposomes. In both patients, autopsy revealed a large proportion of injected radioactivity was still present, predominantly in the liver, spleen, and bone marrow. Within the liver, radioactivity was concentrated predominantly in normal rather than neoplastic tissue. Although further studies are necessary, it is suggested that the use of liposomes as vehicles for selective transport of cytotoxic drugs will be of limited value until the uptake by the liver, spleen, and bone marrow can be prevented. (14 refs)

161. INTRA-ARTICULAR LIPOSOMAL THERAPY.

Thomas DP, Phillips NC
Strangeways Res. Lab., Worts' Causeway, Cambridge, England
Lysosomes in Applied Biology and Therapeutics Vol. 6. Dingle JT, Jacques PJ, Shaw IH, ed. Amsterdam, North-Holland Publishing Co., Frontiers of Biology, Vol. 48, 719 pp., 1979.

Preliminary experiences with intra-articularly administered liposomal drug therapy for control of inflammatory changes within the joints are summarized. Methods, considerations, selection of therapeutic agents, and results obtained with different substances are described. Preliminary data indicate that liposomes are suitable vehicles for the introduction of cytotoxic agents such as daunorubicin into the joint cavity. (23 Refs)

162. LYMPHATIC ABSORPTION AND TISSUE DISPOSITION OF LIPOSOME-ENTRAPPED [14C]ADRIAMYCIN FOLLOWING INTRAPERITONEAL ADMINISTRATION TO RATS.

Parker RJ, Hartman KD, Sieber SM
Lab. Chemical Pharmacology, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(4):1311-1317 1981

The lymphatic absorption and tissue distribution of free [14C]Adriamycin, 'empty' [3H]liposomes, free [14C]Adriamycin plus empty [3H]liposomes, and [14C]Adriamycin entrapped into [3H]liposomes have been examined at intervals after ip injection into rats. Following treatment with empty [3H]liposomes, almost 30% of the liposomal lipid marker was recovered in 24-hr thoracic duct lymph, but when [14C]Adriamycin was added to or encapsulated in liposomes, this value was reduced to 10%. Conversely, only 1% of free [14C]Adriamycin was recovered in 24-hr lymph, but liposomal encapsulation produced a 6-fold increase in this value. Studies on the tissue distribution of the liposomal lipid marker after dosing with empty liposomes revealed uptake by diaphragm, liver, and spleen, but the highest tissue concentrations were noted in lymph nodes. Liposomal encapsulation of Adriamycin altered its tissue disposition, chiefly by increasing the concentration of drug equivalents in diaphragm, liver, and spleen. Although free Adriamycin was accumulated by lymph nodes to some extent, this lymph node accumulation was markedly enhanced by liposomal encapsulation and was present only in those nodes through which lymph draining the peritoneal cavity passes. This finding, together with the observation that diaphragm and thoracic duct lymph contain relatively high levels of liposomal lipid and Adriamycin equivalents, indicates that liposomes are selectively absorbed from the peritoneal cavity by lymphatics and are retained by certain lymph nodes. The results of this study suggest that ip administration of liposome-encapsulated drugs may provide a means of selectively concentrating antitumor agents in lymphatic channels and lymph nodes. (Author abstract) (36 Refs)

163. EFFECT OF THE ROUTE OF ADMINISTRATION ON THE TISSUE DISTRIBUTION OF LIPOSOME-ENCAPSULATED ADRIAMYCIN IN RATS (MEETING ABSTRACT).

Parker RJ, Sieber SM
NIH, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 21:280 1980

The tissue distribution and lymph node uptake of liposome encapsulated 14C-adriamycin (adr) administered to rats by ip and iv routes were compared. Regardless of the route of administration, the uptake of adr by liver and spleen was increased 2-10 fold by liposomal encapsulation at 4 and 24 hr posttreatment; in contrast, liposomal encapsulation decreased adr uptake by heart, lung, skeletal muscle, kidney and gut 2-6 fold after either ip or iv dosing. Drug levels in these tissues were up to 3x higher after iv than after ip dosing at 4 hr after treatment, although at 24 hr tissue levels were approx 2x higher in ip treated rats than in rats dosed by the iv route. The most striking difference between ip and iv routes with regard to tissue distribution was found in diaphragm and lymph nodes. Following an ip dose of free adr,

drug levels in diaphragm and mediastinal lymph nodes were higher by factors of 10 and 75, respectively, than in corresponding plasma at 4 and 24 hr after dosing, and this accumulation was increased 4-fold by liposomal encapsulation. In contrast, free adr administered by the iv route did not accumulate in either diaphragm or lymph nodes, and liposomal encapsulation reduced the uptake of adr in these tissues by 25-50% at 4 and 24 hr after dosing. These results raise the possibility of attaining increased drug concentrations in diaphragmatic lymph channels and in lymph nodes by utilizing the ip route for drug administration; moreover, they indicate that liposomal encapsulation further increases drug uptake into lymphatic channels and lymph nodes following ip, but not iv, dosing. (no Refs)

164. FATE OF LIPOSOME-ENTRAPPED 14C-ADRIAMYCIN (14C-ADR) GIVEN BY IP INJECTION TO RATS (MEETING ABSTRACT).

Parker RJ, Dixon R, Sieber SM
NIH, Bethesda, MD, 20014
Proc Am Assoc Cancer Res; 20:238 1979

Lymphatic drainage is known to be an important mechanism for the removal of particulate matter, including normal and neoplastic cells, from the peritoneal cavity. We are investigating the possibility of increasing the concentration of antitumor agents in lymphatic channels by administering the agents, entrapped in liposomes, by ip injection. Rats with indwelling cannulae in the thoracic duct and femoral artery were given an ip injection of either free 14C-adr or 14C-adr entrapped in multilamellar liposomes (phosphatidyl choline/cholesterol/stearylamine, 5:2:1 by wt), and the levels of 14C-activity in thoracic duct lymph (TDL) and plasma determined at intervals thereafter. Following an ip injection of free 14C-adr, levels of radioactivity in TDL were 1.5-3.0 x higher than levels in plasma at corresponding times up to 24 hr after dosing; when liposome-entrapped 14C-adr was injected, TDL contained 5-30-fold higher levels of 14C activity than did corresponding plasma samples. An av of 5.7% and 3.4% of the administered radioactivity was recovered in 24 hr urine of rats injected with free and entrapped 14C-adr, respectively. Results of comparative studies on the tissue distribution of free vs entrapped 14C-adr indicate thus far that higher levels of radioactivity are present in heart, brain and kidney of rats injected with free 14C-adr than with liposome-entrapped drug. Our findings suggest that the physiologic disposition of adr administered by ip injection is altered by liposomal entrapment and that liposomal entrappment leads to increased drug levels in lymphatic channels. (no Refs)

165. ADRIAMYCIN ENTRAPMENT IN LIPOSOMES: IN VITRO AND IN VIVO STUDIES (MEETING ABSTRACT).

Forssen E, Tokes Z
Sch. Pharmacy, Dept. Biochemistry, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Proc Am Assoc Cancer Res; 20:188 1979

Adriamycin (Ad) is difficult to entrap within phospholipid vesicles (liposomes) due to its amphiphilic properties. We have developed a double-packing procedure to produce stable, pharmacologically active Ad-liposomes. Ad is first bound to phospholipid by sonicating the drug and a suspension of phosphatidylcholine (PC) for 3 min at 100 watts. This material is then entrapped within liposomes consisting of PC, phosphatidyl serine, and cholesterol. The stability of this drug-vesicle complex has been demonstrated to be about 90% in a 10-hr incubation with human plasma at 37 C under sterile conditions. Free and liposome-entrapped 3H-Ad was administered iv to Swiss Webster mice for organ distribution studies. Liposome entrapment resulted in increased Ad delivery to liver and significantly decreased delivery to brain, heart and kidneys. These observations were made at 1 and 4 hr after drug administration. Ad-liposomes appear less harmful to treated animals than equal doses of the free drug, as judged by measurement of wt gain in long-term high dose regimens. The liposome-entrapped drug retains its cytotoxic activity when tested with L1210 cells under in vitro conditions. The preceeding observations justify further studies to test liposome mediated Ad delivery for altered cardiac and renal toxicities and for inhibition of tumor growth. (no Refs)

166. LIPOSOME ENCAPSULATION OF VARIOUS ANTI-TUMOR DRUGS, AND MOUSE TISSUE DISTRIBUTION OF LIPOSOMAL ADRIAMYCIN (MEETING ABSTRACT).

Rahman YE, Cerny EA, Jonah MM, Dainko JL
Div Biol Med Res, Argonne Natl Lab, Argonne, Il 60439
Fed Proc; 36(3):786 1976

Different classes of anti-tumor drugs have been successfully encapsulated within the aqueous and the lipid phase of liposomes: nitrogen mustard, cyclophosphamide (alkylating agents); methotrexate (folic acid antagonist); puromycin cytarabine (purine and pyrimidine antagonists); actinomycin D, adriamycin , daunomycin (antibiotics); vinblastine and vincristine (alkaloids). Two additional drugs, mitomycin C and cis-dichlorodiamineplatinum (II), can be incorporated only in the aqueous phase of the liposomes. The tissue distribution of adriamycin, encapsulated either in aqueous or lipid phase of liposomes, was compared with that of non-encapsulated adriamycin after i.v injection into mice. After both forms of liposomes, there was a significantly lower concentration (about 1/3) of drug in the heart and intestine, and higher drug concentration in the lungs. Retention of liposome-encapsulated adriamycin in various tissues, determined up to 24 hours after injection, was also considerably prolonged. These results suggest that: 1) the known toxicity of adriamycin to the cardiac muscle and the intestinal epithelium could be alleviated by liposome encapsulation; 2) a single dose of adriamycin administered in liposome-encapsulated form could be therapeutically more effective. (Author Abstract)

167. LIPOSOMAL DELIVERY OF ADRIAMYCIN (MEETING ABSTRACT).

Rahman A, Kessler A, Macdonald J, Waravdekar V, Schein P
Div. Medical Oncology, Vincent T. Lombardi Cancer Res. Center, Georgetown Univ., Washington, DC, 20007
Proc Am Assoc Cancer Res; 20:288 1979

Encapsulation of drugs within liposomes offers a simple and effective means of modifying the pharmacokinetics of a variety of anticancer agents. We have encapsulated adriamycin, an antitumor agent with broad spectrum of clinical activity but treatment-limiting cardiotoxicity, into lipid phase liposomes. Negatively charged liposomes were prepared using phosphatidyl choline (PC), cholesterol (CH), and phosphatidyl serine in a molar ratio of 10:4:1 and postively charged liposomes using PC, CH and stearylamine in a molar ratio of 10:4:3. Mice were injected iv with adriamycin, 4 mg/kg, as free drug or entrapped in positive (+) or negative (-) liposomes. A 6-10 fold increase in plasma concentration was achieved with + and - liposomes respectively when compared with free drug. The area under the plasma concentration-time curve for adriamycin with - liposomes was 9.2 ug/hr/ml, and 5.5. ug/hr/ml with + lipo-

somes; this compared to 0.723 ug/hr/ml with free adriamycin. The peak cardiac uptake with + liposomes, 4.2 ug/g, occurred at 5 min compared to 30 min with - liposomes, 9.3 ug/g, and free drug, 8.1 ug/g. From 10 min to 3 hr the max cardiac concentration of + liposomes was about 1/3 that of - liposomes and free drug. Tissue concentration x time values for liposomal adriamycin was 3 x higher in liver and 5 x higher in spleen compared to free drug. Positive liposomes produced a 2-fold increase of drug uptake in lungs compared to - liposomes and free drug. We conclude that + liposomes can selectively decrease adriamycin concentration in cardiac muscle. Antitumor studies with liposomes are now in progress. (no Refs)

168. INTRACELLULAR FATE AND EFFECT OF LIPOSOME-ENTRAPPED ACTINOMYCIN D INJECTED INTO RATS.

Black CD, Gregoriadis G
Clinical Res. Centre, Watford Rd., Harrow, Middlesex, HA1 3UJ, England
Biochem Soc Trans; 2(5):869-871 1974

Liposome-entrapped actinomycin D(A-D:125 ug/kg, injected into tail veins of rats) resulted in a maximum of 44% of the dose in the liver, compared to 18% when nonentrapped A-D was used. The maximum in the lysosome-rich fraction was 54% of the dose, compared to only 1-2% when nonentrapped A-D was used. Studies on RNA synthesis showed that the A-D carried to the nuclei (24% of the dose) was biologically active. Delivery of drugs by liposomes could decrease uptake by the small intestine and increase liver uptake of these drugs. (8 refs)

169. LIPOSOMES CONTAINING H-ACTINOMYCIN D. DIFFERENTIAL TISSUE DISTRIBUTION BY VARYING THE MODE OF DRUG INCORPORATION.

Rahman Y, Kisieleski WE, Buess EM, Cerny EA
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439
Eur J Cancer; 11(12):883-889 1975

A comparative study was made of actinomycin D (A-D) incorporation either in the aqueous soln between the lipid bilayers of the liposomes (aqueous phase liposomes - APL) or as part of the lipid bi-layers (lipid phase liposomes - LPL), and of nonencapsulated A-D, with emphasis on their distribution pattern in female Carworth Farm mouse tissue after iv injections. 3H-A-D distributions were determined at 15 min and 0.5, 1, 3, 6, 24, and 48 hr after injection of either free A-D, A-D in APL, or A-D in LPL. Disappearance of 3H-A-D from the blood was very rapid: 0.5 hr after injection, the highest level was found with APL, the lowest with LPL. In mice receiving LPL, about 40% of the total injected dose was found in the lungs 0.5 hr after injection, and the high concentration was maintained at least up to 6 hr. Mice given either APL or nonencapsulated A-D had very low concentrations of the drug in the lungs. Initial uptake of 3H-A-D in the spleen was low in all groups, but spleens of LPL-injected mice showed a significant increase in drug concentration at 3 hr, and at 24 hr a peak of about 20% of the total injected dose was reached. LPL-injected mice had a higher uptake in the liver than the other groups; the level was maintained up to 6 hr and then decreased. In the kidneys the highest drug concentration occurred in mice given APL or free A-D; mice given LPL had very low levels. Initial uptake of the drug in bone marrow was similar in all groups, but with LPL, uptake continued to increase for 24 hr, reaching a peak concentration of about 10%. With free A-D and LPL, there was a significant decrease of radioactivity between 24 and 48 hr, but a constant level was maintained with APL. Initial concentration in the intestinal wall with free A-D or APL was about 5 x that with LPL. Radioactivity then decreased, and between 24 and 48 hr the levels were similar in all groups. The increase in spleen and bone marrow LPL was closely correlated with a concomitant decrease in liver and lungs. In vitro, different rates of 3H-A-D release from LPL and APL were shown: LPL released negligible radioactivity up to 4 hr, but APL released more than 60% of total radioactivity within 1 hr. These results show that the tissue distribution of drugs can be modified by liposome encapsulation and also by varying the way of incorporating the drug within the liposomes. Although tissue distribution was similar with both free A-D and APL, drug levels were generally higher with APL. The phenomenon of slow drug release from LPL may be useful in future clinical applications. (14 refs)

170. DRUG ENTRAPMENT IN LIPOSOMES.

Gregoriadis G
Clin. Res. Cent., Harrow, Middlesex, England
FEBS Lett; 36(3):292-296 1973

Male Wistar rats (100-150 g) were given iv inj of 3H-actinomycin D (A-D; 1.5 microg, 3.7 Ci/mmole) or potassium 14C-benzyl penicillin, or an (30microg, 38.2m Ci/mmole) equivalent amount of drugs entrapped in liposomes. The liposome entrapped drugs were prepared by sonicating the drugs in the presence of dipalmitoyl lecithin, cholesterol, and either stearylamine (for A-D) or phosphatidic acid (for penicillin). The behavior of liposome entrapped (125I) human serum albumin (0.21-0.31 mg, 1microCi/mg) was used as a control. Inj of free A-D resulted in its rapid removal from the blood (>99% within 25 min). Radioactivity was partially recovered in the small intestine, liver, and kidney, and, although 2.5 hr later very little of it was left in the liver and kidney, considerable amounts were held by the small intestine (18% of the dose). Entrapment of A-D resulted in a drastically reduced rate of removal from the blood (2.5 after inj. 38% of the dose was still in circulation). Further, there was little radioactivity uptake by the small intestine (<5%) and kidney, there was more radioactivity in the spleen, and radioactivity uptake by the liver increased with time (23% of the dose at 2.5 hr). Liposome entrapment may be a useful technic for directing drugs to specific sites of action. (16 refs)

171. ORGAN-SELECTIVE ACTION OF AN ANTITUMOR DRUG: PHARMACOLOGIC STUDIES OF LIPOSOME-ENCAPSULATED BETA-CYTOSINE ARABINOSIDE ADMINISTERED VIA THE RESPIRATORY SYSTEM OF THE RAT.

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Hosp. Sick Children, Res. Inst., 555 Univ. Ave., Toronto, Ontario, Canada M5G 1X8
JNCI; 63(3):727-731 1979

Free or liposome-encapsulated 3H-cytosine arabinoside (ara-C: 0.01-100 mg/kg; about 10 mg lipid) was instilled at the tracheal bifurcation of Wistar rats. Tissue distribution was studied for up to 24 hr. Free ara-C disappeared rapidly from the lungs (half-life about 20 min) and eventually appeared as labeled metabolites in the urine. Liposome-encapsulated ara-C disappeared slowly from the lungs (half-life about 6 hr); for unknown reasons, the elimination curve seemed to be biphasic. There was little radioactivity in the blood, jejunum, or femoral marrow after instillation of liposome-encapsulated ara-C. The 4-hr urinary excretion of label after administration of free and liposome-encapsulated ara-C was 60% and 27%, respectively. Liposomes (labeled with horseradish

peroxidase) instilled into the lower portion of the trachea apparently entered the lungs and became widely distributed in the larger and smaller airways. Distribution was fairly uniform throughout the lung within 1 hr after intratracheal instillation of liposome-encapsulated ara-C. 14C-Thymidine (dThd) incorporation into DNA was studied in the lungs, femoral marrow, and jejunum 75 min after intratracheal administration of free or liposome-encapsulated ara-C (5 mg/kg). Free ara-C inhibited dThd incorporation to about the same extent (20-40% of control) in all tissues studied. Liposome-encapsulated ara-C markedly inhibited dThd incorporation in the lungs (40% of control), but not the jejunum or marrow (89 and 75% of control, respectively). Liposome-encapsulated ara-C may have a local pharmacologic effect within the lungs after intratracheal instillation, without causing toxic effects in other tissues. This observation may be relevant to the chemotherapy of lung metastases. (18 Refs)

172. CONTROLLED DELIVERY OF AN ANTITUMOR DRUG: LOCALIZED ACTION OF LIPOSOME ENCAPSULATED CYTOSINE ARABINOSIDE ADMINISTERED VIA THE RESPIRATORY SYSTEM.

Juliano RL, McCullough HN
Dept. Pharmacology, Univ. Texas Medical Sch., Houston, TX, 77025
J Pharmacol Exp Ther; 214(2):381-387 1980

The distribution and metabolism of free or liposome-encapsulated, 3H-labeled cytosine arabinoside (ara-C: 0.01-100 mg/kg) after intratracheal administration was studied in male Wistar rats. Multilamellar liposomes consisting of egg phosphatidylcholine, cholesterol, and stearylamine (25:7:1 wt ratio) were used. Free ara-C was rapidly cleared from the lungs (half-time, 40 min), but liposome-encapsulated ara-C remained in the lungs for a prolonged period (half-time, 8 hr). Free ara-C inhibited DNA synthesis in the lungs, intestine, and bone marrow. Similar doses of encapsulated ara-C inhibited DNA synthesis only in the lungs. The selectivity of drug action was comparatively low. The ratios of ED50 values (for DNA synthesis inhibition) for free and encapsulated ara-C were 2.3 in in the lung and 6.0-6.1 in the intestine and bone marrow. The dose-response curves for encapsulated ara-C, instead of being parallel to those for free ara-C, resembled the free ara-C curves at high doses, perhaps because liposome-encapsulated ara-C was osmotically unstable at high ara-C doses. Free and encapsulated ara-C were metabolized to the same products: phosphorylated anabolites of ara-C and an inactive catabolite (uracil-beta-D-arabinofuranoside). It was suggested that the action of an antitumor agent can be confined to one organ system through the use of a liposomal dosage form. (27 Refs)

173. DIFFERENTIAL DISTRIBUTION OF LIPOSOME-ENTRAPPED (H) METHOTREXATE AND LABELLED LIPIDS AFTER INTRAVENOUS INJECTION IN A PRIMATE.

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Biochim Biophys Acta; 448(4):531-550 1976

The distribution of (3H)methotrexate (MTX) entrapped in the internal aqueous space of both positive and negative liposomes is compared with the distribution of (14C)cholesterol and 3H-labeled dipalmitoyl phosphatidylcholine incorporated into the lipid bilayers. The quantitatively different distribution of these labelled compounds suggests the possibility of independent exchange reactions for the lipids occurring in vivo, as well as the lack of any renal excretion of intact liposomes. This study showed a decreased disappearance of 3H from liposome-entrapped (3H)MTX from plasma; MTX, which is rapidly excreted in the free form and shows no appreciable leakage out of liposomes, can obtain a > 50-fold increase in plasma levels when administered as liposome-entrapped rather than as free drug. The increased rate of removal of (14C) cholesterol and (3H) dipalmitoyl phosphatidylcholine, at least for sonicated liposomes, suggests preferential removal of cholesterol and phospholipid by exchange processes that do not affect the basic structural integrity and permeability properties of the liposomes. Selective uptake of 14C into RBC, which was greatest for sonicated liposomes at longer time periods, was also observed. Results of this study clearly indicated the preferential uptake of 14C relative to 3H from liposomes containing (3H) MTX and (14C) cholesterol. Injection of MTX entrapped in liposomes provides two major potential advantages compared with the free form: it maintains high plasma levels necessary for therapeutic action, and entrapment can prevent degradation of a drug. The outstanding problem for potential chemotherapeutic use of liposome-entrapped drugs is ensuring a degree of selective uptake by the target malignant tissues with sparing of normal tissue. (39 refs)

174. DISTRIBUTION OF FREE AND LIPOSOME-ENTRAPPED (H)METHOTREXATE IN THE CENTRAL NERVOUS SYSTEM AFTER INTRACEREBROVENTRICULAR INJECTION IN A PRIMATE.

Kimelberg HK, Tracy TF, Watson RE, Kung D, Reiss FL, Bourke RS
Div. Neurosurgery, Albany Medical Coll. of Union Univ., Albany, NY, 12208
Cancer Res; 38(3):706-712 1978

The distribution of 3H-labeled free methotrexate (MTX) and 3H-MTX entrapped inside sonically disrupted, positively charged (14C)cholesterol-labeled liposomes in the CNS of cynomolgus monkeys was studied after the administration of single MTX injections into the cerebrospinal fluid (CSF) in the lateral cerebroventricles. At 24-96 hr after the injection of liposome-entrapped MTX, the av tissue (brain plus spinal cord) level of 3H-MTX was increased 4 x over that observed during the same period after an injection of free MTX. The injection of liposome-entrapped MTX also resulted in greater levels of MTX in the CSF relative to those after free MTX injection; however, considerable variation in levels was observed according to the sampling site. Metabolic degradation of free MTX was detected 24 hr after injection. At 96 hr postinjection, only 11% of the free MTX in the CSF represented intact MTX compared with 72% for liposome-entrapped MTX injection. Studies of MTX distribution in brain tissue at 24 hr postinjection revealed that 3H-MTX levels after the injection of liposome-entrapped MTX were higher near tissue-CSF interfaces and lower in deep areas of the brain in comparison with levels measured after the injection of free MTX. Considerable leakage of MTX from the CNS to the plasma was found soon after the injection of both forms of MTX, but liposome-entrapped MTX showed 10-20x higher steady-state plasma levels. This was attributed to a much lower rate of removal of MTX from plasma due to the much lower renal excretion of liposome-entrapped MTX. (25 Refs)

175. THE EFFECT OF ENTRAPMENT IN LIPOSOMES ON THE IN VIVO DISTRIBUTION OF (H)METHOTREXATE IN A PRIMATE.

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Cancer Res; 36(8):2949-2957 1976

Entrapment of methotrexate (MTX) plus (3',5', 9(n)-3H)methotrexate into positively charged liposomes greatly alters the subsequent distribution of (3H)MTX in a cynomolgous monkey (Macaca irus) after a single iv injection ((3Hh)MTX; refers to total radioactivity derived from purified (3H) MTX). When (3H)MTX is incorporated into small, sonically disrupted liposomes, the level of the entrapped (3H)MTX in the total plasma volume was still 50% of the total injected dose after 4 hr, which is 100 times greater than the level found when the same amount of free MTX (1 to 4 mg) plus (3H)MTX was injected. When entrapped in larger mechanically dispersed liposomes, however, the plasma levels of liposome-entrapped (3H)MTX at 4 hr was only 6-fold greater than free (3H)MTX. The liposome-entrapped MTX (refers to MTX measured by dihydrofolate reductase assay) did not show detectable breakdown in the plasma whereas free MTX showed up to 97% breakdown. Increased clearance of (3H)MTX entrapped in mechanically dispersed liposomes was complemented by its much greater uptake into tissues, especially spleen, compared with sonically disrupted liposomes. There was over a 160-fold increased uptake by the spleen of liposome-entrapped (3H)MTX relative to free (3H)MTC, whereas for sonically disrupted liposomes the comparable ratio was 20. Although this liposome-entrapped MTX showed significant breakdown, it was less than that found after injection of free MTX. In certain tissues, especially the small intestine, a reduced uptake of liposome-entrapped (3H)MTX was found. Uptake of liposome-entrapped (3H)MTX into liposomes led to a much lower renal clearance of (3H)MTX, especially in the case of sonically disrupted liposomes. Possible reasons for these effects and the relationship of our findings to those of others are discussed. (Author Abstract)

176. THE CARRIER POTENTIAL OF LIPOSOMES FOR METHOTREXATE. CHANGES IN THE TISSUE LEVELS OF METHOTREXATE IN THE ORGANS OF MICE.

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Z Krebsforsch; 90(2):187-195 1977

NMRI mice were injected with liposome entrapped methotrexate (MTX) and the variations in MTX tissue levels in the organs were investigated. Female mice (15) were injected with a 0.5 ml of liposomal 3H-MTX soln in the tail vein. Groups of three mice were killed with nitrogen after 10, 30, or 60 min or 3 or 6 hr, and the liver, spleen, kidneys, gut and lungs were immediately removed and the radioactivity determined. A control group of 15 mice were injected with free 3H-MTX. The enrichment factors of entrapped MTX vs free MTX after iv injection were 0.5 after 60 min and 8.4 after 6 hr in the intestine, 4.1 after 60 min and 19.2 after 6 hr in the liver, and 5.3 after 60 min and 11.5 after 6 hr in the kidney. (10 Refs)

177. LIPOSOMES AS CARRIERS IN VIVO FOR METHOTREXATE.

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Biochem Soc Trans; 3(1):157-159 1975

The preferential uptake of methotrexate (MTX) entrapped in liposomes (phospholipid vesicles) by various organs of male Wistar rats was studied. When MTX was added to liposomes composed of egg phosphatidylcholine, cholesterol, and dicetyl phosphate (molar ratio 5:5:1), which carries a net negative charge, 18% MTX entrapment was found at final lipid concn of 100 mg/ml. Tail-vein inj of rats with 1 ml of a soln containing 1 mg/ml MTX (including 0.25 uCi 3H-MTX) entrapped in liposomes (4 mg lipid/ml) showed that entrapment markedly decreased the rate of clearance of MTX from the blood. The concn in liver and spleen were increased, but that of the kidney was decreased. Substitution of stearylamine, for dicetyl phosphate in the lipid (now bearing a net positive charge), showed an increased proportion of lipid uptake by the liver and spleen. Neutral lipid appeared to be taken up preferentially by the spleen. It is concluded that further investigation of the effects of lipid composition on uptake may lead to liposomes that are taken up more efficiently and that may be directed to target tissues, facilitating selective delivery of drugs to the target tissue. (3 refs)

178. EFFECTS OF ENTRAPMENT IN LIPOSOMES ON THE DISTRIBUTION, DEGRADATION AND EFFECTIVENESS OF METHOTREXATE IN VIVO (MEETING ABSTRACT).

Kimelberg HK, Archison ML

Albany Medical Coll., Albany, NY

Conference on Liposomes and Their Uses in Biology and Medicine Seminar held in New York, N Y, September 14-16, 1977 The New York Academy of Sciences, New York, NY, 1977.

Methotrexate (MTX) was entrapped inside positively charged liposomes and injected into primates (Macaca fasicularis) and mice. Its pharmacokinetics, metabolism and effectiveness against L1210 tumor cells in vivo was compared with that of free MTX. MTX entrapped in sonicated liposomes disappeared from the plasma much more slowly than free MTX, and unlike free MTX there was no breakdown of liposome-entrapped (H3)MTX to H3-labelled non-MTX products. Increased uptake of liposome-entrapped MTX into tissues, especially liver and spleen, was observed and it seems that the decreased disappearance from plasma was mainly due to inhibition of renal excretion. Double-label studies suggested that exchange of cholesterol can occur independently of liposome uptake. Liposome-entrapped MTX was no more effective than free MTX at increasing the survival time of DBA/2 mice bearing L1210 cells, and for some types of liposomes was more toxic. It seems that increased effects that can occur with 'non-targeted' liposome-entrapped drugs may be due to a long-term depot effect of the liposomes for drugs whose levels are reduced much more rapidly than MTX in mice. (no Refs)

179. PHARMACOKINETICS OF LIPOSOME-ENCAPSULATED ANTI-TUMOR DRUGS. STUDIES WITH VINBLASTINE, ACTINOMYCIN D, CYTOSINE ARABINOSIDE, AND DAUNOMYCIN.

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Research Inst., Hosp. for Sick Children, Toronto, Ontario M5G 1X8, Canada
Biochem Pharmacol; 27(1):21-27 1978

The effects of liposome encapsulation on the plasma clearance kinetics and tissue disposition of four anti-tumor drugs were investigated. Adult male rats (280-350 g) were injected iv with actinomycin D (A-D), vinblastine (VLB), cytosine arabinoside (ara-C), or daunomycin (DN), either as the free drug (5-50 ug) or in a liposome-encapsulated form (1-5 ug of drug). Plasma clearance of the free drug was biphasic in all cases, with a rapid initial first phase (half-times, less than 2-5 min) and a much slower second phase. After liposome encapsulation, plasma clearance curves for all drugs were similar. Plasma clearance was greatly retarded: 10-40% of the drug was cleared with a half-time of about 8-10 min, and the bulk of the drug was cleared very slowly (half-time, about 150-200 min). Tissue distributions (liver, spleen, lung, kidney, brain, intestine, muscle, and heart) of H-labeled VLB, A-D, and ara-C were studied. The favored uptake sites for free A-D were spleen, intestine, lung, and kidney; for free VLB, these were spleen, intestine, and lung. Hepatic uptake of free A-D or VLB was comparatively low. After liposome encapsulation, the greatest tissue uptake of A-D and VLB was in the liver and spleen. Encapsulated ara-C was more widely distributed in the viscera than encapsulated VLB or A-D. With ara-C, only the liver showed a significant increase in uptake when the drug was given in liposome-encapsulated form. Tissue uptake of DN was studied by fluorimetric analysis; results of preliminary studies indicated that liposome encapsulation increased DN uptake about 10x in various tissues. Liposome encapsulation also caused a marked increase in the total amount of drug equivalents retained by the tissues at various times; for liposome-encapsulated ara-C, this increase was 68x for hepatic retention at 16 hr after injection. (36 Refs)

180. ENCAPSULATION OF ANTICANCER DRUGS IN LARGE-VOLUME LIPOSOMES AND DISTRIBUTIONS IN VIVO (MEETING ABSTRACT).

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Lab. Chemotherapy, Aichi Cancer Center, Chikusa-ku, Nagoya 464, Japan
Proceedings of the 37th Annual Meeting of the Japanese Cancer Association held in Tokyo, Japan, August, 1978. Japanese Cancer Association Tokyo, Japan, 283 pp., 1978.

The nature of large-vol liposomes (DB-L), prepared by the method of Deamer and Bangham, and that of anticancer agents encapsulated in DB-L were studied. DB-L were prepared from phospholipid obtained by mixing phosphatidylcholine and phosphatidylserine at a 9:1 ratio. Anticancer agents chosen were cytosine arabinoside (CA), ifosfamide, and adriamycin (ADR). Their in vivo distribution was investigated using BDF1 mice. DB-L encapsulated about 10 x as much CA as liposomes prepared by the conventional methods did, although there was no significant difference between DB-L and liposomes for ADR. When encapsulating CA or not, DB-L had a hollow structure of 2 to 10 umeters in size, which was demonstrated by electron microscopy with negative stain. When encapsulating ADR, DB-L had a multilamellar structure, similar to those of liposomes. DB-L encapsulating CA were rather stable for 24 hr after preparation. DB-L remained in lymph nodes and lungs for a long time. (no Refs)

181. LIPOSOMES AS VEHICLES FOR THE LOCAL RELEASE OF DRUGS.

Segal AW, Gregoriadis G, Black CD
Div. Clin. Invest., Clin. Res. Cent., Harrow, Middlesex, England
Clin Sci Mol Med ; 49(2):99-106 1975

An investigation of the possible use of liposomes for the delayed local release of drugs is reported. Liposomes were prepared from solutions of egg lecithin (160 umole) and cholesterol (46 umole) in chloroform containing phosphatidic acid (23 umole) or L-hexadecylamine (23 umole); small sonicated liposomes had a lipid content of 1-5 g/l, while large unsonicated liposomes contained 1.5-8.5 g/l. Albino Sprague-Dawley rats were inj in the left testis with 50 ul of liposome-entrapped radio-labeled albumin (0.04 umole/ml), actinomycin D (355 umole/ml), or 5-fluorouracil (0.076 umole/ml) and in the right testis with an equal amount of nonentrapped material, then sacrificed and assayed for testicular radioactivity. Large unsonicated liposomes significantly delayed the release of entrapped albumin over a 24-hr period, with a greater delay in neutral than charged liposomes; after 24 hr, 84.8% of the lipsome radioactivity and 49.8% of the albumin radioactivity remained in the testis, 5.7% of the albumin radioactivity was in the serum, and 0.5% of each was in the liver; with negatively charged sonicated liposomes most of the radioactivity was eliminated from the testis at 24 hr, and was found predominantly in the liver, serum, spleen, and lungs, although it had disappeared from a draining lymph node that had accumulated 2% of the albumin radioactivity at 10 min. Entrapment of actinomycin D in unsonicated positive liposomes markedly delayed elimination from the testes, while entrapment in sonicated negative liposomes enhanced the rate of loss (54.7% residual radioactivity at 24 hr) but also resulted in accumulation of high levels in draining lymph nodes (11-fold greater than the free drug). Elimination of 5-fluorouracil was similarly delayed by entrapment in unsonicated positive liposomes. Actinomycin D (0.1-50 ug) in unsonicated neutral liposomes retained its cytotoxicity for seminiferous tubules, resulting in focal dose-dependent tissue necrosis. It is concluded that large unsonicated liposomes remain localized and slowly release their contents, whereas small sonicated liposomes are rapidly dispersed to sites including draining lymphatics where they are degraded. (13 refs)

182. PENETRATION OF TARGET AREAS IN THE RAT BY LIPOSOME-ASSOCIATED BLEOMYCIN, GLUCOSE OXIDASE, AND INSULIN.

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FEBS Lett; 63(2):235-239 1976

Small and large liposomes were used to entrap In-bleomycin and I-polyvinylpyrrolidone, and their uptake by liver and tumor were measured. After i.v inj of labeled BLEO, both normal liver and two murine tumors (6C3HED intrascapularly and Meth "A" on the kidney of BABC/c mice) took up considerably more radioactivity when BLEO had been entrapped in liposomes than when admin free. Uptake by tumors was greatest when small liposomes were used, and liver uptake was greatest when larger liposomes were used, presumably because of the decreased rate of elimination of small liposomes from the circulation. I.p admin of labeled polyvinylpyrrolidone entrapped in liposomes was followed by uptake of radioactivity by the liver regardless of the liposome size, but following i.m admin small liposomes appeared to reach the circulation more quickly. Following intragastric admin of labeled polyvinylpyrrolidone, 98% of

the label was recovered in the feces, but small amounts were taken up by the liver, and significantly increased amounts were taken up when the drug was admin entrapped in liposomes. Glucose oxidase had a minimal effect on blood glucose when given intragastrically in its free form or when associated with negative and positive egg lecithin liposomes, and negative results were obtained with intragastrically admin insulin, either free or with those same liposomes. However, when glucose oxidase was admin in association with phosphatidyl inositol liposomes blood glucose levels decreased considerably, and when insulin was admin in association with phosphatidyl inositol liposomes there was a marked reduction in blood sugar. It is implied that these results may be of interest in improving the delivery of drugs to difficult target areas. (22 refs)

183. PENETRATION OF TARGET AREAS IN THE RAT BY LIPOSOME-ASSOCIATED AGENTS ADMINISTERED PARENTERALLY AND INTRAGASTRICALLY.

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Biochem Soc Trans; 4(2):256-259 1976

The transport of liposome-associated agents to liver and tumor tissue after admin by various routes in mice is described. Model target areas were: malignant tissues (6C3HED cells implanted in the intrascapular area of C3 H mice, Meth "A" malignant tissue in the left kidney of Balb/c-mice) approached by the i.v route; liver and spleen approached i.p; and circulating blood approached by the intragastric route. 111In-bleomycin (2.5 mCi), glucose oxidase (200 mg), insulin (160 U), and 125I-polyvinylpyrrolidone (10 uCi) were entrapped in liposomes composed of egg phosphatidylcholine and cholesterol (neutral, molar ratio 7:2) with or without phosphatidic acid (negative) or stearylamine (positive, molar ratio 7:2:1). Mice were killed 24-48 hr after inj of 111In-bleomycin, free or entrapped liposomes, into the tail vein. Radioactivity was greatest in liver and tumor when the entrapped drug was used (32.8 and 3.92% of dose/g tissue, resp, compared to 1.18 and 1.81%, resp, when free drug was admin). The foregoing values were obtained using liposomes (sonicated 30 sec) in C3H mice, similar values being observed with BALB/c mice. Sonification for 20 min. (smaller liposomes) gave 25.6 and 6.82% of the dose/g tissue, resp in C3 H mice. After i.p admin of 125I-polyvinylpyrrolidone to Sprague-Dawley rats, 32 and 5% of the inj dose was recovered in the liver and spleen, resp, but analogous values after inj of free drug were only 6.9 and 1%. After intragastric admin of free 125I-polyvinylpyrrolidone, > 98% of the radioactivity was recovered in the feces, and hepatic uptake was only 0.07%. This was increased to 0.17% after admin of liposome-associated agent. Glucose oxidase (5 mg/kg i.v) decreased blood glucose by > 90% in 15 min in rats, but when given intragastrically, either free or entrapped in negative and positive liposomes, it was without effect. Phosphatidylinositol liposome-associated insulin intragastrically admin, resulted in considerable reduction of blood sugar compared to the minimal effect of free insulin. Phosphatidylinositol liposome-associated glucose oxidase was also effective intragastrically. (6 refs)

184. INCORPORATION OF CIS-DICHLOROBISCYCLOPENTYLAMINEPLATINUM (II) INTO LIPOSOMES ENHANCES ITS UPTAKE BY ADJ/PC6A TUMOURS IMPLANTED SUBCUTANEOUSLY INTO MICE.

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Biochem Soc Trans; 5(5):1326-1328 1977

Mice with 26-day-old sc ADJ/PC6A tumors were inoculated iv with cis- dichlorobiscyclopentylamineplatinum (II) (340 ug), either free or incorporated into egg phosphatidylcholine (PDC) or dipalmitoyl PDC liposomes. After the free drug was injected, very little was taken up by the tumor (0.15% of the dose/g) 1 or 3 hr later. The plasma concentration after 1 hr was 0.74% of the dose/ml, indicating rapid clearance by the spleen. When the drug was given as a liposome complex, participation of the tumor in uptake increased; this increase was 15-fold when egg PDC liposomes were used. Egg PDC liposomes had an advantage over dipalmitoyl PDC liposomes in that drug uptake by the liver was smaller with the former. It is concluded that incorporation into liposomes can overcome the insolubility of this compound in organic solvents. (5 Refs)

B.

Pharmacokinetics of liposome-encapsulated radiopharmaceuticals

185. RADIATION BIOLOGY AND POTENTIAL THERAPEUTIC APPLICATIONS OF RADIONUCLIDES.

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Bull Cancer (Paris); 67(3):343-353 1980

Recent advances in basic radiobiological research and in the synthesis of tumor-seeking compounds have produced renewed interest in the possibility of cancer therapy with unsealed radionuclides (RN). In a review of recent developments, discussions are presented of choice of RN, and choice of delivery systems. Ideally, internal therapy should be performed with shortlived RN which emit high linear energy transfer (LET) radiation to insure a high relative biological effectiveness and a low oxygen enhancement ratio. In addition, the emitted radiations should have a range of no more than a few cell diameters in order to minimize damage to surrounding normal tissues. Such radionuclides should accumulate within cancers, or at least exhibit diverse chemical properties to facilitate the development of tumor-specific radiopharmaceuticals. No known radionuclide fulfills all these requirements. However, some of the criteria are met by the alpha particle emitter astatine-211 and by several RN which decay by electron capture and Auger emission, for example iodine-125 or iodine-123. The key problem remains the development of agents which can serve as carriers for selective radionuclide accumulation within tumors. Approaches which may become useful in selected types of tumors include the use of Synkavit, tamoxifen, iododeoxyuridine, liposomes, and tumor-specific antibodies. (69 Refs)

186. TISSUE DISTRIBUTION AND TUMOR LOCALIZATION OF 99M-TECHNETIUM LABELLED LIPOSOMES IN CANCER PATIENTS.

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Dept. Biochemistry, Charing Cross Hosp. Medical Sch., Univ. London, Fulham Palace Road, London, W6 8RF, England
Br J Cancer; 40(1):35-43 1979

The possible use of liposomes (phospholipid vesicles) to direct cytotoxic drugs to tumors had led us to investigate the tissue localization of iv injected 99m-Tc-labeled liposomes in cancer patients. Twenty mg or 30 mg doses of liposomal lipid (7:2:1 molar ratio of phosphatidylcholine:cholesterol:phosphatidic acid) were used in a study of 13 patients with advanced cancer and one with polycythemia rubra vera (PRV). In all cases except the patients with PRV the major site of uptake of the label was the liver and spleen. In the patient with PRV the liver uptake was greatly reduced and the major site of uptake was found to be in regions corresponding to marrow. With the exception of one patient with a primary hepatoma, there was no significant tumor uptake of the label. (Author abstract) (33 Refs)

187. 99MTC-LABELLED LIPOSOME PREPARATION OF RADIOPHARMACEUTICAL AND ITS DISTRIBUTION IN A HEPATOMA PATIENT.

Richardson VJ, Ryman BE, Jewkes RF, Tattersall MH, Newlands ES
Dept. Biochemistry, Charing Cross Hosp. Medical Sch., Fulham Palace Road, Hammersmith, London, W6 8RF, England
Int J Nucl Med Biol; 5(2/3):118-122 1978

The use of 99mTc-labeled liposomes as a radiopharmaceutical in a 44-yr-old woman with primary hepatoma is described. A phosphatidylcholine liposome suspension (50 mg of lipid in 0.9% saline), prepared under strict sterile conditions and tested for pyrogenicity and sterility, was labeled with 5 mCi of technetium and injected iv into the patient. A series of pictures were made at 1 min intervals for 30 min and further pictures were taken at less frequent intervals for 2 hr. A final picture was taken after 24 hr. Subsequently, conventional liver scan studies using technetium colloid and 123I Rose Bengal were performed. The distribution of radioactivity in the hepatic region remained virtually identical from 16 min to 24 hr after the injection. The normal outline of the right lobe of the liver was seen and the right and left lobes spanned a mass in the midline of the upper abdomen corresponding to the palpable tumor. At 24 hr, a slight reduction of radioactivity over the tumor area was recorded. There appeared to be little or no localization in the area of the tumor. The tumor appeared as 'cold' and similar to the conventional iodine Rose Bengal scan. (15 Refs)

188. DISTRIBUTION OF [99MTC]TECHNETIUM-LABELLED LIPOSOMES IN PATIENTS WITH CANCER (MEETING ABSTRACT).

Richardson VJ, Jeyasingh K, Jewkes RF, Kaye SB, Newlands ES, Ryman BE, Tattersall MH
Dept. Biochemistry, Charing Cross Hosp., London, England
Br J Cancer; 38(1):195 1978

Liposomes (phospholipid vesicles) have been proposed as carriers of antitumor drugs in order to alter the blood clearance, tumor and marrow localization of the drugs and thereby increase their therapeutic value. Gamma-Camera studies have shown that 99mTc (technetium) label attached to small anionic liposomes concentrates in the Walker 256 carcinoma model. We have now studied the distribution of 99mTc-labeled liposomes in 14 patients with advanced cancer and one patient with polycythemia rubra vera (PRV). Pharmaceutical preparations of liposomes, 20 or 30 mg of lipid (7:2:1 molar ratio phosphatidylcholine:cholesterol:phosphatidic acid) labeled with approx 20 milliCi of 99mTc, were injected iv. Blood clearance and urine excretion of the label were measured over 24 hr, and the tissue distribution at 24 hr was observed using a whole-body scanner. In all cases, excluding the patient with PRV, the major site of uptake of the label was the liver and spleen. In the patient with PRV, liver and spleen uptake were greatly reduced and the majority of the radioactivity was found in sites corresponding to the marrow. With the possible exception of one patient with a hepatoma, there was no evidence of tumor localization of radioactivity. The interesting results in the patient with PRV may reflect the altered marrow turnover which occurs in this condition. Future plans include a study on larger numbers of patients using liposomes of different sizes and lipid compositions. (1 Ref)

189. DRUG-CARRIER POTENTIAL OF LIPOSOMES IN CANCER CHEMOTHERAPY.

Gregoriadis G, Wills EJ, Swain CP, Tavill AS
Clin. Res. Cent., Middlesex, England
Lancet; 1(7870):1313-1317 1974

The possibility of using liposomes as drug carriers was studied in 3 patients with metastatic carcinomas using 131I labeled serum albumin trapped in the liposomes as a marker for determining their disappearance from plasma and uptake by the tissues. Liposomes were prepared from dipalmitoyl lecithin, cholesterol, and phosphatidic acid and sterile human serum-albumin by sonication; after removal of nonentrapped protein 131I was attached to the albumin by the iodine monochloride method. During the study the thyroid gland was blocked with potassium iodide (60 mg 2x/d, po); liposomes were admin is in 1 patient, and iv in 2 patients. Blood samples were taken at various intervals after inj. Hepatic uptake of radioactivity was measured using the hybrid scanner technique. Tissue samples for radioassay and electron microscopy were obtained in 1 patient 3 hr after inj and in a second patient 5 d after inj. More than 80% of the labeled liposomes disappeared from the plasma within 6 hr; rapid removal was accounted for by early uptake into the liver (81% in 1 patient). There was no evidence of uptake by bone marrow. In the tissue samples examined, tissues other than liver had taken up liposomal albumin; levels of radioactivity in tumors were higher than normal tissue (50 X higher in primary renal tumor than normal renal tissue). Catabolism of albumin was also greater in tumor than normal tissue. With electron microscopy liposomes were seen in cytoplasmic vacuoles of 1/3 of liver parenchymal cells, were sometimes seen in autophagic vacuoles of parenchymal cells, and were uncommon in Kupffer's cells. A few liposomes were seen in primary and metastatic tumor cells and occasionally in macrophages within the primary tumor. (14 refs)

190. APPROACHES TO TUMOUR LOCALIZATION WITH TECHNETIUM 99M LABELLED LIPOSOMES (MEETING ABSTRACT).

Jewkes RF, Jeyasingh K, Richardson V
Dept. Nuclear Medicine, Charing Cross Hosp., London W6, England
Br J Radiol; 52(621):762 1979

Liposomes of different charges, negative phosphatidylcholine (P):cholesterol (C):dicetylphosphate, 7:2:1), neutral (P:C, 8:2) and positive (P:C:stearylamine (S), 7:2:1) were la-

beled with 99Tcm on the lipid membrane, and their in vivo distribution studied in normal rats and in two rat tumor models. Wistar rats bearing inguinal Walker 256 carcinomas received iv liposomes. Negative liposomes localized appreciably in the tumors (1-2% dose/g at 24 hr) and the tumors could be demonstrated by scintigraphy. Positive liposomes showed marginally lower tumor uptake while the tumor uptake of neutral liposomes was negligible. Small liposomes were better localized than large liposomes. Rats bearing Rd/3 tumors in a foot pad with regional lymph node metastases received liposomes by interstitial injection close to the primary tumor. Normal rats were similarly injected in a foot pad. At 5 hr there was uptake of radioactivity in the lymph nodes which could be clearly seen scintigraphically. Positive and negative liposomes gave uptake in the primary lymph node of about 1% and 0.3% of the dose, respectively. This was not significantly altered by the presence of secondary tumor. Neutral liposomes showed marked reduction in uptake in the presence of metastases. Technetium-labeled liposomes were given by iv injection to 12 patients with advanced solid tumors and 2 patients with hematological malignancies. The liposomes concentrated predominantly in the liver and bone marrow in all cases except one of polycythemia rubra vera which was remarkable in that bone marrow uptake was not associated with liver accumulation. Only one case (a hepatoma) showed detectable radioactivity in the tumor. Common human tumors clearly differ significantly from the rapidly growing experimental rat tumors. This suggests that even when liposome composition has been optimized, uptake of liposomes will vary with tumor type, rate of growth and any previous treatment. We see no likelihood of liposomes becoming an effective tumor-seeking radiopharmaceutical unless they can be directed specifically, perhaps by the incorporation of antitumor antibodies into their structure. (no Refs)

191. POSSIBLE TUMOR LOCALIZATION OF TC-99M-LABELED LIPOSOMES: EFFECTS OF LIPID COMPOSITION, CHARGE, AND LIPOSOME SIZE.

Richardson VJ, Jeyasingh K, Jewkes RF, Ryman BE, Tattersall MH
Dept. Biochemistry, Charing Cross Hosp. and Medical Sch., Fulham Place Road, London W6 8RF, England
J Nucl Med; 19(9):1049-1054 1978

The possible in vivo distribution of liposomes after they have been directly labeled with Tc-99m has been studied in rats bearing the Walker 256 carcinoma. The importance of lipid composition, charge, and size of lipososome were studied with respect to possible tumor-localizing properties. Tumor uptake was best with small, fluid-membrane, negatively charged liposomes, as indicated by the distribution of the Tc-99m label. The uptake was visualized on scintigrams. (Author abstract) (15 Refs)

192. DIFFERENTIAL LOCALIZATION OF [MTC]TECHNETIUM-LABELLED LIPOSOMES IN NORMAL AND TUMOUR-BEARING LYMPH NODES OF THE RAT (MEETING ABSTRACT).

Richardson VJ, Osborne MP, Jeyasingh K, Ryman BE, Burn JI
Dept. Biochemistry, Charing Cross Hosp. Medical Sch., London, England
Br J Cancer; 38(1):177 1978

Using the rat Rd/3 foot-pad tumor model, a differential localization of interstitially-injected 99mTc-labeled liposomes (phospholipid vesicles) in the primary regional lymph nodes (PRLN) with and without tumor infiltration has been observed. The results obtained with small negative [7:2:1, phosphatidylcholine (PC):cholesterol (C):phosphatidic acid], positive [7:2:1, PC:C:stearylamine] and neutral [8:2, PC:C] liposomes at 5 and 30 hr after injection are given. Our findings suggest that 99mTc-labeled neutral liposomes may be a suitable lympho-scintigraphic agent for the detection of lymph node metastases, since a marked suppression of uptake of label was observed with neutral liposomes when comparing normal and tumor-infiltrated PRLN (P less than 0.01 at 5 hr and less than 0.005 at 30 hr). Cationic liposomes may potentially be useful as carriers of therapeutic agents for the treatment of lymph node metastases as these liposomes localize well in both normal and tumor-infiltrated PRLN. (1 Ref)

193. SATURATION OF UPTAKE OF LIPOSOMES BY THE RETICULOENDOTHELIAL SYSTEM: POSSIBLE USE FOR INCREASED TUMOR SPECIFICITY (MEETING ABSTRACT).

Haynes DH, Kang CH
Dept. Pharmacology, Univ. Miami Medical Sch., Miami, FL 33152
Conference on Liposomes and Their Uses in Biology and Medicine Seminar held in New York, N. Y, September 14-16, 1977 The New York Academy of Sciences. New York, NY, 1977.

Liposomes injected into the mammalian blood stream are taken up by the liver and spleen, the site of uptake most probably being the cells of the reticuloendothelial system (RES). This is a major drawback to the use of liposomes as drug carriers and we have looked for ways to inhibit this RES function. Liposomes were prepared by sonication of egg PC in the presence of H3 inulin and were separated from unilamellar vesicles and untrapped marker by elution with a Sepharose 4B column. When 10 mg of such liposomes are injected into the tail vein of a rat, and the distribution is analyzed after 60 min, only 15% of the liposomes remain in the blood stream while 55% are taken up by the liver. Hepatic uptake can be reduced by preinjection with unlabelled liposomes. Preinjection with 300 mg of unlabelled egg PC liposomes 30 min prior to the injection of labelled liposomes, followed by sacrifice 60 min later showed that about 70% of the total injected radioactivity remained in the blood stream while only 10% was taken up by the liver. The kinetics of this inhibition of the RES and its application to tumor-bearing rats are discussed. (no Refs)

194. PULMONARY LOCALIZATION OF INTRAVENOUSLY INJECTED LIPOSOMES.

Fidler IJ, Raz A, Fogler WE, Poste G
Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
Recent Results Cancer Res; 75:246-251 1980

The effects of liposome size, surface charge, and composition on the tissue distribution of liposomes injected iv into female BALB/c mice were investigated, with particular attention given to the factors affecting accumulation of liposomes in the lung. Multilamellar vesicle (MLV), reversed evaporation phase vesicle (REV), large unilamellar vesicle (LUV), and small unilamellar vesicle (SUV) liposomes were used. The large MLV liposomes were cleared from circulation more quickly than small sonicated SUV liposomes, and negatively charged liposomes were cleared more rapidly than neutral or positively charged liposomes of the same size. Liposomes containing 125I-bovine serum albumin (125I-BSA) circulated as intact structures and were incorporated into tissues intact. MLV and LUV liposomes composed entirely of phosphatidylserine (PS) achieved the highest level of accumulation in the lung, but their value as carriers was limited by their toxicity. Optimal lung retention without toxicity was obtained with MLV and REV liposomes containing smaller amounts of PS plus phosphatidyl-

choline. The amount of 125I-BSA encapsulated in MLV or REV liposomes retained in the lung after iv injection was between 35% and 40% of that retained in the liver. When expressed as the percentage of injected 125I-BSA retained/g tissue, the retention of PS-containing liposomes in the lung exceeded that in the liver. (8 Refs)

195. RADIOLABELED LIPOSOMES AS METABOLIC AND SCANNING TRACERS IN MICE. II. IN-111 OXINE COMPARED WITH TC-99M DTPA, ENTRAPPED IN MULTILAMELLAR LIPID VESICLES.

Espinola LG, Beaucaire J, Gottschalk A, Caride VJ
Yale Univ., New Haven, CT
J Nucl Med; 20(5):434-440 1979

We describe the organ distribution of positively and negatively charged multilamellar lipid vesicles (MLV) labeled with Tc-99m diethylenetriaminepentacetic acid (DTPA) or In-111 oxine in mice. The organ distribution of MLV (In-111 oxine) is fairly constant throughout 72 hr, indicating that the radiotracer remains associated with cellular structures at the site of MLV uptake. In animals injected with MLV (Tc-99m DTPA), on the other hand, there is continuous leakage of radioactivity from the involved organs. This can be explained by the release of the radiotracer following MLV destruction in the organs. MLV (IN-111 oxine) may be used to study MLV uptake by different organs, whereas MLV (Tc-99m DTPA) may be a good indicator of the destruction rate of lipid vesicles. Various conditions bearing on liposome kinetics merit further study in order to assess the potentialities of these vectors as diagnostic or therapeutic agents. (Author abstract) (13 Refs)

196. INVESTIGATIONS OF A NEW, HIGHLY NEGATIVE LIPOSOME WITH IMPROVED BIODISTRIBUTION FOR IMAGING.

Hnatowich DJ, Clancy B
Dept. Nuclear Medicine, Univ. Massachusetts Medical Center, Worcester, MA, 01605
J Nucl Med; 21(7):662-669 1980

An attractive feature of liposomes is the wide range of lipid composition that can lead to liposome formation, coupled with the observation that liposome biodistribution may be altered by varying lipid composition. For instance, adding charged lipids to neutral lecithin will alter the biodistribution of the resulting charged liposomes. We have prepared highly negative liposomes by replacing lecithin with negatively charged cardiolipin. The liposomes have been labeled in the lipid phase with Ga-67 and Tc-99m oxime and their properties evaluated. The expected high negative charge of the resulting liposomes was confirmed by an ion-exchange chromatographic technique. Using paper chromatography, the stability of the label was determined during incubation in saline and serum. Finally, biodistributions were determined at 2 hr in mice, and the results compared with those for negative lecithin liposomes. Accumulated activities in liver and spleen were reduced by factors of 5 and 20, respectively, over lecithin liposomes. Since preferential accumulation of activity in these organs constitutes the biggest limitation to the use of lecithin liposomes, cardiolipin liposomes may prove to be more useful carriers of radioactivity in imaging applications. More importantly, however, these results illustrate the value of studying novel liposome types as potential radiopharmaceuticals. (Author abstract) (22 Refs)

197. AVAILABILITY OF LIPOSOME CONTENT TO THE NERVOUS SYSTEM. LIPOSOMES AND THE BLOOD-BRAIN BARRIER.

Tokes ZA, Todd JA, Kulcsar StPeteri A
Dept. Biochemistry, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Brain Res; 188(1):282-286 1980

The ability of hydrophilic molecules entrapped in artificial lipid-bilayer vesicles to cross the blood-brain barrier was studied in mice. In the first set of experiments, fluorescent labeled albumin, 6-carboxyfluorescein, or trypan blue was entrapped in liposomes and iv injected. Tissue sections of the brain that were examined later showed pronounced staining of the brain capillaries. None of the entrapped substances penetrated anatomical regions of neural origin. The second set of experiments utilized the neurotropic agents, methylbicucullin, serotonin, and gamma-aminobutyric acid; these agents were also iv injected after encapsulation in liposomes. These experiments further indicated that the liposome-entrapped material did not become available to the CNS. In the third set of experiments, the bacterium, Bordetella pertussis, was used to increase the barrier permeability. Even under these conditions, liposomes did not penetrate to the neural elements of the CNS. A transport mechanism for lipophilic molecules across the blood-brain barrier was proposed. (19 Refs)

198. LIPOSOMES AND THE BLOOD BRAIN BARRIER (MEETING ABSTRACT).

Tokes ZA, StPeteri AK
Dept. Biochemistry, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
J Cell Biol; 79(2,part2):102a 1978

Since lipophilic substances readily pass through the blood brain barrier, we have raised the question whether hydrophilic molecules entrapped in liposomes would also be carried through the barrier. Three sets of experiments were designed with Swiss-Webster mice. In the first set fluorescent labeled albumin and trypan blue were entrapped in liposomes and sections from brain were examined after iv injections. The second set utilized the neurotropic agents methylbicuculline, serotonin and gamma-aminobutyric acid (GABA), which normally do not cross the barrier. Mice were pretreated with pargyline to enhance the response to serotonin or with 3-mercaptopropionic acid to decrease endogenous GABA levels. In the third set Bordetella pertussis was used to artificially increase the permeability. Liposomes were prepared from phosphatidylcholine (PC):cholesterol (Ch) 9:1, from PC:stearylamine:Ch 20:2:15, from sphinogomyelin:Ch 9:1, or from mouse brain lipid extract and Ch. After sonication liposomes were purified on Sephadex G-100 column or by washing and centrifugation. Increased staining of the brain capillaries was observed with liposomes; however, none of the entrapped substances penetrated anatomical regions of neural origin. Methylbicuculline, a GABA antagonist, in liposomes produced clonic convulsions within 30 sec of intracranial administration. However, 100-fold greater quantities introduced iv failed to promote any neurologic syndrome. Similarly, serotonin liposome complexes (55 mg/kg) produced no effect on CNS. Action on peripheral nervous tissue was observed. Increased permeability produced by B pertussis failed to increase permeability to liposomes. These experiments demonstrate that the content of liposomes becomes available to the synaptic regions in the CNS when injected intracranially. There is no evidence that their content can enter through the barrier, suggesting that lipophilic substances enter

through a discriminating route which may be narrow and restrict the entrance of entrapped hydrophilic material. (no Refs)

C.
In vivo effects of liposome-encapsulated antitumor agents

199. IN VITRO AND IN VIVO STUDIES WITH ADRIAMYCIN LIPOSOMES.

Forssen EA, Tokes ZA
Sch. Pharmacy, Univ. Southern California, Los Angeles, CA
Biochem Biophys Res Commun; 91(4):1295-1301 1979

Adriamycin (Adr) was bound to phosphatidylcholine (PC) by adding the drug to the lipid and then sonicating. The resulting drug-lipid mixture was entrapped within either anionic liposomes consisting of a 7:3:1 molar ratio of PC, cholesterol (Ch) and phosphatidyl serine, or cationic liposomes containing PC, Ch, and stearylamine at ratio of 7:3:0.5. The liposome suspensions were sonicated, and unentrapped Adr separated out by Sephadex gel filtration. Between 5-10% of the starting Adr was entrapped. Swiss mice were injected via the tail vein with Adr in either free or entrapped form. Mice were sacrificed at 1 and 4 hr after drug administration and the brain, heart, kidneys, liver, lungs, and spleen removed and submitted to liquid scintillation spectrometry using tissue solubilizer. Murine leukemia L-1210 Moore cells were also treated with free and liposome-entrapped Adr. Control cells were untreated or treated with free Adr or with empty anionic liposomes. A high dose toxicity study was performed using Swiss mice. Liposome-entrapped Adr retained its full cytotoxic potential when tested under in vitro conditions against murine leukemia L-1210 cells. In vivo drug studies indicated that a lower proportion of liposome-entrapped Adr was delivered to the brain, heart, lung, and kidneys as compared to the free drug at both 1 and 4 hr, but an increased proportion was delivered to the liver reflecting active removal by the reticuloendothelial system. Mice receiving 10 mg/kg iv free or entrapped Adr showed less wt loss and greater final wt gain after 10 wk with entrapped Adr than with free. (12 Refs)

200. LIPOSOMAL PROTECTION OF ADRIAMYCIN-INDUCED CARDIOTOXICITY IN MICE.

Rahman A, Kessler A, More N, Sikic B, Rowden G, Woolley P, Schein PS
Div. Medical Oncology, Georgetown Univ. Hosp., 3800 Reservoir Road, N.W., Washington, DC, 20007
Cancer Res; 40(5):1532-1537 1980

The pharmacological and therapeutic effects of adriamycin entrapped in positively charged and negatively charged liposomes were compared with those of free adriamycin in mice. Liposomes were composed of phosphatidylcholine and cholesterol mixed with stearyl amine (positive charge) or phosphatidylserine (negative charge). Positive liposomes with entrapped adriamycin effectively retarded the in vivo uptake of drug in cardiac tissue when compared to free drug or drug entrapped in negative liposomes. At 4 mg/kg iv, the peak drug concentration in heart occurred in 30 min following administration of free adriamycin or adriamycin entrapped in negative liposomes, compared to 5 min with adriamycin entrapped in positive liposomes. The max drug concentration achieved with positive liposomes in cardiac tissue was approx one-half that of free drug or drug entrapped in negative liposomes. In addition, the cardiac concentration time values for adriamycin administered in positive liposomes were considerably less than that of free drug or negative liposomes for the 24-hr period of observation. The liposomal adriamycin was preferentially concentrated in liver, spleen, and lungs. Electron microscopic studies demonstrated that the myocytes and myofibrillar structure of cardiac muscle were markedly well preserved with adriamycin in positive liposomes, in contrast to the two other delivery forms. The antitumor activity of the drug against murine ascitic P388 leukemia and Lewis lung carcinoma demonstrated an identical effect when administered as free drug or entrapped in positive liposomes. The specific positively charged liposome developed in these studies selectively reduces the acute cardiotoxicity of adriamycin without loss of antitumor activity. (Author abstract) (26 Refs)

201. INVESTIGATION OF SOME HAEMATOLOGICAL PARAMETERS IN TUMOR BEARING MICE TREATED WITH LIPOSOME ENCAPSULATED BLEOMYCIN.

Sur P, Hazra B, Roy DK
Dept. Pharmacy, Jadavpur Univ., Calcutta 700032, India
IRCS Med Sci: Cancer; 8(11):844-845 1980

Hematologic parameters were studied in normal male Swiss A mice (N group), in mice inoculated with 2 x 10(5) Ehrlich ascites carcinoma (EAC) cells (C group), and in EAC-treated mice given free bleomycin (1.5 mg/kg/day for 16 days: B group) or liposome-trapped bleomycin (1.5 mg/kg/day for 16 days: L group). RBC counts were similar in the N, C, B, and L groups, but the WBC count of the C group was 120% higher than that of the N group. The WBC count was significantly elevated over control levels in the B group also, although the elevation was less than that in the C group, and the WBC count in the L group was similar to that in the N group. Neutrophils were drastically increased in the C group as compared with the N group, less drastically increased in the B group, and not significantly increased in the L group. Thus, chemotherapy with negative liposomes appears to offer a better means of treatment than the use of free bleomycin. (5 Refs)

202. ENHANCEMENT OF THE ACTION OF BLEOMYCIN USING LIPOSOMES WITH EHRLICH'S ASCITES CARCINOMA IN MICE.

Sur P, Roy DK
Dept. Pharmacy, Jadavpur Univ., Calcutta 700 032, India
Indian J Exp Biol; 17(9):952-953 1979

The actions of bleomycin (BL, 2 mg/kg/day, ip, for 10 days) and BL (1.5 mg/kg/day, ip, for 10 days) combined with liposomes (BLL) on Ehrlich ascites tumors of Swiss A mice were studied. Survival time was increased in mice treated with BLL compared with those treated with BL. When BL (0.75 mg/kg/day) in liposomes was given for 20 days, 75% of the mice were cured and the remaining 25% lived longer than those treated with BL (1 mg/kg/day) alone for 20 days. (12 Refs)

203. ANTITUMOR EFFECT OF NEOCARZINOSTATIN ENTRAPPED IN NEUTRAL, NEGATIVELY AND POSITIVELY CHARGED LIPOSOMES AGAINST EHRLICH SOLID CARCINOMA.

Shinozawa S, Araki Y, Oda T
Dept. Hosp. Pharmacy, Okayama Univ. Medical Sch., Shikata-cho 2-5-1, Okayama 700, Japan
Res Commun Chem Pathol Pharmacol; 30(1):181-184 1980

The antitumor effects of free neocarzinostatin (NCS) and of NCS entrapped in sonicated liposomes (neutral, negatively charged, or positively charged) were compared in dYY mice bearing solid Ehrlich carcinoma. Antitumor effects were monitored by determining tumor areas at different

times during treatment and tumor wt after termination of treatment. Mice were treated with five ip injections of free NCS, liposome-entrapped NCS, or physiological saline (controls) on day 12, 14, 16, 18, and 20 after inoculation with cancer cells. On day 17, the mean tumor area in mice treated with free NCS was 4.20 +-0.47 square cm (cm2); significantly smaller mean tumor areas were observed in mice treated with NCS in neutral liposomes (2.99 +-0.38 cm2) or with NCS in negatively charged liposomes (2.85 +-0.44 cm2). Statistically significant differences were observed in tumor areas of mice treated with free NCS and mice treated with NCS in neutral liposomes on day 19 and 21 and between tumor areas of mice treated with free NCS and mice treated with NCS in negatively charged liposomes on day 21. The mean tumor wt calculated on day 22 were as follows: 5.27 +-0.63 g in the control group, 4.19 +-1.07 g in mice treated with free NCS, 4.02 +-0.87 g in mice treated with NCS in positively charged liposomes, 2.62 +-0.46 g in mice treated with NCS in negatively charged liposomes, and 1.55 +-0.27 g in mice treated with NCS in neutral liposomes. (16 Refs)

204. ANTITUMOR EFFECT OF NEOCARZINOSTATIN ENTRAPPED IN LIPOSOMES.

Shinozawa S, Araki Y, Oda T
Dept. Hosp. Pharmacy, Okayama Univ. Medical Sch., Shikata-cho 2-5-1, Okayama 700
Gan; 71(1):107-111 1980

Antitumor effect against mouse Ehrlich ascites carcinoma was examined on neocarzinostatin(NCS) entrapped in sonicated liposomes (neutral and negatively or positively charged forms) in comparison with free NCS. In the ip inoculation-ip medication system, NCS entrapped in negatively charged liposomes, which was most unstable in aqueous soln, showed statistically significant prolongation of survival days in mice compared to free NCS. In contrast, survival days of the animals given NCS entrapped in positively charged liposomes were shorter than those of the corresponding groups given free NCS. On the other hand in the ip inoculation-iv medication system, survival days were not prolonged markedly by administration of free NCS, but when NCS was entrapped in positively charged or neutral liposomes, prolongation of survival was apparent compared to the corresponding groups given free NCS. The most marked effect was seen when NCS was entrapped in positively charged liposomes, which show the best stability in aqueous soln. (Author abstract) (20 Refs)

205. ANTITUMOR EFFECT OF ILLUDIN-S (LAMPTEROL) ENTRAPPED IN LIPOSOMES FOR MICE INOCULATED WITH EHRLICH ASCITES TUMOR CELLS.

Shinozawa S, Tsutsui K, Yabe M, Araki Y, Oda T
Dept. Biochemistry, Cancer Inst. Okayama Univ., Medical Sch., Shikata-cho, Okayama 700, Japan
Igaku Ayumi; 108(7):414-416 1979

Male ddN strain mice (6-wk-old, 20-24 g) were inoculated ip with 2 x 10(7) cells/0.2 ml suspension/mouse of Ehrlich ascites tumor cells. After 24 hr, mice were divided into groups of 10 mice each. Mice were administered aqueous soln of free Illudin-S in a single dose of 83.0, 166.0, 333.0, or 800.0 ug/kg in Group A, Illudin-S entrapped in liposomes in a dose of 16.5, 83.0, 166.0, 333.0, or 800.0 ug/kg in Group B, and physiological saline soln in Group C as a control, and the effect on prolongation of life was examined. The entraption rate of Illudin-S in liposomes was 9.3%. The longest mean survival period in Group A was 15.79 +-8.40 (days +- standard deviation) at 166.0 ug/kg, and the percentage of the mean survival period at 166.0 ug/kg dose of Group A to those of Group C was 170%. The mean survival period at 20.97 +-7.36 at 166.0 ug/kg dose and 26.65 +-11.10 at 333.0 ug/kg dose in Group B, and the percentage of the mean survival period of Group B to those of Group C was 225% at 166.0 ug/kg dose and 287% at 333.0 ug/kg dose. More than 50% of the mice survived over 25 days at 333.0 ug/kg dose in Group B. Therefore, the side effect decreased and antitumor effect increased by the use of Illudin-S entrapped in liposomes. (10 Refs)

206. ENHANCEMENT OF THE ANTITUMOR EFFECT OF ILLUDIN S BY INCLUDING IT INTO LIPOSOMES.

Shinozawa S, Tsutsui K, Oda T
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Experientia; 35(8):1102-1103 1979

Male ddN mice bearing 1-day-old ascites Ehrlich carcinoma were treated with single ip doses of an aqueous soln of illudin S (ILL-S), an antitumor agent prepared from Lampteromyces japonicus. The ILL-S was administered either in free form or liposome-encapsulated (egg yolk, cholesterol and stearylamine in a 3.2:2.2:1 molar ratio). After the treatment with the free ILL-S, the greatest increase in the treated/control (T/C) survival time ratio (170%) was at a concentration of the agent of 166 ug/kg, with 1/10 long-term survivors (LTS: 25 days). In mice given liposome-encapsulated ILL-S, the T/C ratio was 225% at 166 ug/kg (2/10 LTS) and 287% at 333 ug/kg (6/10 LTS). The mechanism of action of ILL-S is not clear, but the agent markedly inhibited RNA synthesis (without reducing protein synthesis) in cultures of L929 or chick embryo cells. The evaluation of ILL-S has been limited by its toxicity (such as damage to the liver and hemorrhage of the gastrointestinal tract, kidneys, and lungs). Liposome encapsulation apparently reduced the toxicity of ILL-S without diminishing its antitumor activity. It is suggested that the slow release of ILL-S from liposomes increases the contact between the liposomes and tumor cells while minimizing normal tissue damage, thereby increasing the affinity of ILL-S for tumor cells and potentiating its antitumor activity. (11 Refs)

207. EFFECT OF ACTINOMYCIN D-CONTAINING LIPID VESICLES ON MURINE RENAL ADENOCARCINOMA.

Kedar A, Mayhew E, Moore RH, Williams P, Murphy GP
Dept. Experimental Surgery, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 15(4):363-365 1980

Forty Balb C/CR mice inoculated with renal cell adenocarcinoma were divided into five groups. Group A (7 animals) received phosphate buffered saline ip; Group B (7 animals) received free actinomycin D, 300 ug/kg ip; Group C (9 animals) received lipid vesicles containing actinomycin D, 300 ug/kg ip; Group D (8 animals) received a mixture of free actinomycin D, 300 ug/kg and empty lipid vesicles ip. The median survival of Group A was 32 days, of Group B 30 days, of group C 45.2 days, of Group D 54 days, and of Group E 42 days. It is suggested that giving the mixture of the drug and the lipid vesicles produces a balance similar to that found in a vesicle soln containing the actinomycin D. It is also suggested that liposomes slow the absorption of actinomycin D from the peritoneum. (Author abstract) (10 Refs)

208. THE FATE OF LIPOSOME-ENTRAPPED ACTINOMYCIN D IN VIVO AND ITS THERAPEUTIC EFFECT IN A SOLID MURINE TUMOUR.

Kaye SB, Ryman BE
Dept. Medical Oncology, Charing Cross Hosp., Fulham Palace Road, Hammersmith, London W6 8RF, England
Biochem Soc Trans; 8(1):107-108 1980

Liposome-entrapped actinomycin D (AMD: 5 ug/g, iv) was administered to groups of six mice killed at intervals up to 24 hr later. Liposomes containing AMD underwent gradual disruption in the circulation, and released drug became associated with albumin. In AKR mice bearing the Ridgway osteosarcoma, free AMD (0.3 ug/g) had inhibited tumor growth to 10% of control tumor wt 10 days after treatment, whereas liposome-entrapped AMD (less than or equal to 8 ug/g) inhibited tumor growth to only 68% of control tumor wt. The LD50 values for free and liposome-entrained AMD were 0.8 and 8 ug/g, respectively. (7 Refs)

209. EFFECT OF LIPOSOME ENCAPSULATION OF ACTINOMYCIN-D ON ITS THERAPEUTIC EFFICACY (MEETING ABSTRACT).

Kaye SB, Boden JA, Bagshawe KD, Ryman BE
Dept. Medical Oncology and Biochemistry, Charing Cross Hosp., London, England
Br J Cancer; 40(5):819 1979

Liposomes (phospholipid vesicles) are capable of prolonging the plasma clearance, modifying the tissue distribution and enhancing the in vitro activity of cytotoxic agents, and have therefore been proposed as drug carriers. We have compared the efficacy of actinomycin D (AD) encapsulated in small cationic liposomes with that of free drug, in a combined therapeutic-toxicity study. The model used was the Ridgway osteosarcoma (ROS) maintained by serial passage in AKR mice. For free AD the minimum effective dose (MED: the dose which inhibited tumor growth to 10% of control tumor wt) was 0.3 mg/kg, and the LD50 was 0.8 mg/kg. In contrast, with iv doses up to 8 mg/kg of AD encapsulated in liposomes, neither the MED nor the LD50 have been reached. The max tumor-growth inhibition was 68% of control tumor wt, while survival of mice treated with 8 mg/kg of entrapped drug was 83%. These results indicate that, despite a considerable delay in plasma clearance (the 5 hr plasma level of AD was 3-7 fold greater for entrapped than for free drug) the activity of AD encapsulated in liposomes in both host and tumor tissues is markedly reduced. This may partly be due to failure of drug uptake, since the peak ROS tumor AD concentration (expressed as percentage of injected dose per g of tumor at 24 hr) was 6.0% +-0.5 (mean +- standard error) for free AD, and 2.0% +-0.2 for entrapped AD. Further studies should determine whether liposome encapsulation of cytotoxic drugs may prove more useful for the treatment of drug-resistant tumors, or for those drugs whose activity is enhanced by delayed plasma clearance. (no Refs)

210. PROLONGED SURVIVAL OF TUMOUR-BEARING MICE TREATED WITH LIPOSOME ENTRAPPED ACTINOMYCIN D.

Neerungjun DE, Gregoriadis G
Clin. Res. Cent., Middlesex, England
Biochem Soc Trans; 2(5):868-869 1974

The possible use of liposomes as drug carriers for cancer chemotherapy was studied on a model system, namely the spontaneous lymphoma of AKR mice. This model was chosen because of its similarity to human lymphoid leukemia. The ip injection of 10(6) AKR-A cells in AKR mice caused tumors and death in 9-12 days. Mice inj with AKR-A cells were treated 2-6 days later with actinomycin D (0.5 or 1.0 ug), or with actinomycin D (0.5 or 1.0 ug) entrapped in the lipid phase of a suspension of liposomes composed of egg lecithin, cholesterol, or phosphatidic acid, or with liposomes alone. Actinomycin D alone caused an increase in survival time from 9-12 days to 12-22 days. The inj of 1.0 ug of actinomycin D entrapped in liposomes, every 2 days for 10 days, beginning 3 days after the AKR-A tumor cell inj, caused an increase in survival time to 18-22 days. By contrast, mice treated with non-entrapped actinomycin D under the same conditions survived for 12-14 days. Entrapped actinomycin D was nontoxic to Staphylococcus albus and was therefore not released into the medium. Entrapment of actinomycin D into liposomes resulted in the avoidance of adverse drug reactions and increased efficiency against the AKR-A tumor in AKR mice. The system is of potential use in the treatment of human leukemias. (8 refs)

211. MECHANISMS OF REDUCTION OF ANTITUMOR DRUG TOXICITY BY LIPOSOME ENCAPSULATION (MEETING ABSTRACT).

Rahman YE, Hanson WR, Bharucha J, Ainsworth EJ, Jaroslow B
Argonne Natl. Lab., Argonne, IL
Conference on Liposomes and Their Uses in Biology and Medicine Seminar held in New York, N Y, September 14-16, 1977 The New York Academy of Sciences, New York, NY, 1977.

Actinomycin D (Act. D), when encapsulated within liposomes, was shown to be less toxic to mice than nonencapsulated Act. D, but retain its efficacy against the growth of tumor cells (Rahman et al., 1974; Gregoriadis and Neerunjun, 1975). We have compared the toxic effects of liposome-encapsulated and nonencapsulated Act. D. in the blood-forming system, on cell proliferation in the intestine, and on antibody production by spleen lymphocytes. At a single dose of 0.4 mg/kg, liposome-encapsulated Act. D was less toxic to WBC and to nucleated cells and colony-forming units of the bone marrow. Drug toxicity in the proliferating intestinal cells, measured by H3-thymidine incorporation, was reduced by about a factor of 4 with encapsulation, particularly 24 hr after Act. D administration. Effects of Act. D on the antibody production by spleen cells, determined by the 'limited hemolysis in agar' assay, show that immunosuppression was most markedly reduced by liposome encapsulation when the drug was given one day before the antigen. These findings are important for considerations of liposome application in cancer chemotherapy. (no Refs)

212. LIPOSOME-ENCAPSULATED ACTINOMYCIN D; POTENTIAL IN CANCER CHEMOTHERAPY (MEETING ABSTRACT).

Rahman YE, Cerny EA, Tollaksen SL, Wright BJ, Nance SL, Thomson JF
Div. Biol. Med. Res., Argonne Natl. Lab., Argonne, Ill.
Proc Soc Exp Biol Med; 146(4):1173-1176 1974

Non-encapsulated (NE-) and liposome-encapsulated (LE-) actinomycin-D (AD) were admin to female CF *ERR21*mice inj with 20 x 10(6) Ehrlich ascites tumor cells. In experiment I, controls received 0.4 ml of 8 mM CaCl(2), a second group of 0.75 mg/kg NE-AD and a third group 0.75 mg/kg LE-AD. In experiment II, treatment was LE-AD, 0.50 mg/kg on d 4 + 0.25 mg/kg on d 5-8 and controls received CaCl(2) on a similar schedule. LD(50) for AD inj iv was 0.43 mg/kg. Animals were observed for at least 24 d. No deaths were observed in mice admin. LE-AD iv (1mg/kg) or ip (2 mg/kg) and no drug toxicity was manifested. For experiment I, av survival time (AST) was in-

creased from 7.4 d in controls to 13.2 d. AST of mice receiving NE-AD was slightly, but not significantly, less than the untreated controls. Following multiple inj of LE-AD, AST increased to 17.6 d vs. 7.3 d in controls. NE-AD was too toxic to be used in this regime. LE-AD was found within Ehrlich cells 1 hr after inj. Severe tumor cell damage, degeneration and death were noted soon thereafter in electron microscopic studies. The underlying mechanism for this reduction in toxicity and increase in AST with LE-AD is not understood but tentative suggestions are offered. The preparation of LE-AD is described. (13 refs)

213. THE EFFECT OF LIPOSOME (PHOSPHOLIPID VESICLE) ENTRAPMENT OF ACTINOMYCIN D AND METHOTREXATE ON THE IN VIVO TREATMENT OF SENSITIVE AND RESISTANT SOLID MURINE TUMOURS.

Kaye SB, Boden JA, Ryman BE
Dept. Medical Oncology, Charing Cross Hosp. and Medical Sch., Fulham Palace Road, London, W6 8RF, England
Eur J Cancer; 17(3):279-289 1981

When tested in mice bearing the Ridgway osteosarcoma (ROS) the activity of methotrexate entrapped in small cationic liposomes was increased, both in terms of tumor growth inhibition and toxicity for normal tissues. Conversely, actinomycin D entrapped in small cationic liposomes lost its cytotoxic activity, both against the tumor and normal tissues. In addition, liposome-entrapped actinomycin D proved ineffective therapeutically against a new ROS tumor subline in which resistance to free drug had been derived in vivo; moreover, this resistance appeared to have resulted from failure to retain drug rather than through impaired drug uptake. These results, and those obtained from tissue distribution studies using free and liposome-entrapped actinomycin D, suggested that (a) liposome entrapment modifies the pharmacokinetics and hence activity of these drugs by acting as a slow release system rather than by providing a means of selective delivery to tumors, and (b) the use of liposome-entrapped actinomycin D to overcome drug resistance acquired in vivo may be inappropriate. (Author abstract) (40 Refs)

214. APPLICATION OF LIPOSOME-ENTRAPPED CYTOTOXIC DRUGS TO THE TREATMENT IN VIVO OF DRUG-RESISTANT SOLID MURINE TUMORS (MEETING ABSTRACT).

Kaye SB, Boden JA, Ryman BE
Dept. Medical Oncology, Charing Cross Hosp. Medical Sch., London, W6 8RF, England
Proc Am Assoc Cancer Res; 21:254 1980

Previous studies have shown that both methotrexate (MTX)-resistant solid tumors in vivo and transport defective actinomycin-D (AD)-resistant tumor cells in vitro could be rendered sensitive by treatment with liposome-entrapped drugs. These properties of liposomes have been further examined in combined therapeutic-toxicity studies in vivo using AKR mice bearing the MTX-resistant Ridgway osteogenic sarcoma (ROS). The activity of MTX entrapped in small cationic liposomes was generally enhanced, with an eight-fold reduction in the dose required to produce equivalent degrees both of tumor growth inhibition and host toxicity, compared to free drug. There was no improvement in the therapeutic index of MTX. Conversely AD in small cationic liposomes (lip AD) proved ineffective therapeutically against a new subline of the ROS tumor in which AD resistance had been derived in vivo; at the doses tested it also proved nontoxic compared to free drug. Drug disposition studies in vivo using 3H-AD indicated that (a) liposome entrapment does not result in any selective drug delivery to tumors, but rather it prolongs drug exposure at a low level (compared to free AD) both of tumor cells and of sensitive normal tissues; (b) the AD resistance acquired in vivo appeared to have resulted from a failure of drug retention rather than through a failure of drug uptake, as assessed by AD concentrations in sensitive and resistant tumor following (free) drug injection. The use of lip AD to overcome this form of drug resistance may therefore be inappropriate. (2 Refs)

215. ENHANCEMENT OF CHEMOTHERAPEUTIC EFFICACY OF METHOTREXATE ENTRAPPED IN LIPOSOMES AGAINST MURINE INTRACRANIAL L1210 LEUKEMIA (MEETING ABSTRACT).

Woo SY, Dilliplane DP, Sinks LF
Georgetown Univ. Hosp., Washington, DC, 20007
Proc Am Assoc Cancer Res; 21:307 1980

Mice bearing ascitic or intracranial L1210 leukemia were tested with liposomal methotrexate (MTX), free MTX, and saline. Single ip injections of liposomal MTX at doses of 5 mg/kg and 2.5 mg/kg, and injections of free MTX at 5 mg/kg prolonged survival of intracranial as well as ascitic L1210 leukemia bearing mice. For intracranial L1210 liposomal-MTX was significantly superior to the free drug in each dose category. (no Refs)

216. EFFECT OF LIPID VESICLE (LIPOSOME) ENCAPSULATION OF METHOTREXATE ON ITS CHEMOTHERAPEUTIC EFFICACY IN SOLID RODENT TUMORS.

Kosloski MJ, Rosen F, Milholland RJ, Papahadjopoulos D
Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263
Cancer Res; 38(9):2848-2853 1978

The effects of free methotrexate (MTX) and MTX encapsulated in positively charged unilamellar phospholipid vesicles (liposomes) derived from egg yolk (SUV-MTX) were studied in P1798 S/B (Burton line) cortisol-sensitive mouse lymphosarcoma and Murphy-Sturm rat lymphosarcoma (MSL). In suspensions of the MTX-resistant cell line (P1798 S/B), the uptake of H-MTX (10**-6 M) was 54% greater with SUV-MTX than with free MTX. In mice with established solid tumors, SUV-MTX (1.0 mg/kg/day x 8, ip) caused an 80% reduction in tumor mass. Free MTX had no effect against P1798 S/B at this dose and a 5x higher dose was less effective than 1.0 mg/kg/day of SUV-MTX. In MSL cells (MTX-sensitive), H-MTX (10**-6 M) uptake was 2.6x greater with SUV-MTX than with free MTX. In rats with established solid tumors, SUV-MTX (0.5 mg/kg/day x 8) caused 82% tumor regression compared with 52% for free MTX. It is concluded that encapsulation of MTX in lipid vesicles enhances its association with tumor cells in vitro and improves the response of solid rodent tumors to MTX treatment. (42 Refs)

217. EFFECT OF LIPOSOME-ENTRAPPED METHOTREXATE ON EHRLICH ASCITES TUMOR CELLS AND UPTAKE IN PRIMARY LIVER CELL TUMOR.

Freise J, Schmidt FW, Magerstedt P
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J Cancer Res Clin Oncol; 94(1):21-27 1979

Methotrexate (MTX) entrapped in artificial liposomes was tested for its effect on Ehrlich ascites tumor cells in NMRI mice. The uptake of the entrapped MTX by liver cells and

primary liver cell tumor in Wistar rats was also investigated. For the tests on the Ehrlich tumor cells, ascites fluid containing tumor cells (0.5 ml) was injected ip in 52 mice (12 wk old, 28-32 g). After 72 hr, Groups I-IV of 13 mice each were injected daily for 5 days as follows: Group I, 0.5 ml 0.9% NaCl, iv; II, 0.25 mg MTX in 0.5 ml 0.9% NaCl, iv; III, 0.25 mg entrapped MTX in 0.5 ml 0.9% NaCl, iv; and IV, 0.25 mg entrapped MTX in 0.5 ml NaCl, ip. Results obtained with Groups I and II showed that the effect of free MTX given iv on the production of ascites fluid and tumor cell count was not different from that of NaCl alone. (Two mice in group II died). In Group III, the entrapped MTX given iv caused a significant reduction in ascites fluid and tumor cells. In Group IV, given entrapped MTX ip, all mice died within 24 hr. For the tests on the normal liver cells and liver tumor cells, primary liver tumor was induced in rats by diethylnitrosamine (20 mg/kg body wt weekly, 22 wk, ip). Two groups of 10 rats not bearing induced liver tumor were injected iv with tritiated MTX (0.5 mg in 1 ml 0.9% NaCl), using entrapped MTX in one group and free MTX in the other. The free MTX was maximal (10% of injected dose) in the normal liver cells in less than 30 min and was approx 1/3 that of the entrapped MTX; the entrapped MTX was maximal (35% of injected dose) at 1 hr and at that time was approx 4 x the free MTX; at 6 hr, the entrapped MTX (15% of injected dose) was approx 20 x the free MTX. In seven rats bearing the primary liver cell tumor, the radioactivity of the entrapped MTX was predominantly found in the normal liver tissue. Generally, little MTX uptake was detected in the borderline tissue of the tumor and even less in the central tissue. (11 Refs)

218. ROLE OF LIPOSOME TYPE AND ROUTE OF ADMINISTRATION IN THE ANTITUMOR ACTIVITY OF LIPOSOME-ENTRAPPED 1-BETA-D-ARABINOFURANOSYLCYTOSINE AGAINST MOUSE L1210 LEUKEMIA.

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Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 39(4):1390-1395 1979

The antitumor activity of cytosine arabinoside (ara-C) entrapped in liposomes of different sizes and net surface charges was investigated in L1210 tumor-bearing mice and L1210 cells in culture. The liposomes were composed of phosphatidylcholine and cholesterol mixed with either phosphatidylserine (negative charge) or stearylamine (positive charge). The data indicated that multilamellar vesicles (MLV) were much more effective in trapping ara-C than were small unilamellar vesicles (SUV) and that MLV containing ara-C were more effective than SUV or large unilamellar vesicles (LUV) against L1210 tumors at comparable doses. The antitumor activity of LUV (composed of pure phosphatidylserine) was limited by host toxicity. Positively and negatively charged MLV were equally effective in vivo. Entrapped ara-C was active against L1210 tumors when the tumor transplant and treatment were carried out by the iv route. For example, when mice were injected with 10(6) L1210 cells iv on day 0 and given an iv dose of 50 mg/kg of ara-C entrapped in negatively charged MLV 24 hr later, the tumor/control survival value was 197% compared with only 111% for mice receiving the same dose of free ara-C. The fact that liposome-entrapped ara-C was effective against L1210 tumors even when 10(6) cells were injected shows that liposomes are effective even at high tumor loads. Mice bearing L1210 iv and treated po with entrapped ara-C had longer survival times than mice treated with liposomes only. Acute toxicity tests showed that liposomes alone had no adverse effect on the host, even at very high levels (greater than 5,500 mg lipid/kg on day 1). The data also showed that ara-C entrapped in lipid vesicles was more toxic than free ara-C. (39 Refs)

219. EFFICACY OF LIPOSOME-ENTRAPPED CYTOSINE ARABINOSIDE (ARA-C) COMPARED WITH INFUSED 'FREE' ARA-C AGAINST L1210 TUMOR (MEETING ABSTRACT).

Mayhew E, Rustum Y, Szoka F
Roswell Park Memorial Inst., Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 21:293 1980

1-beta-D-Arabinofuranosylcytosine (ARA-C) is usually administered clinically by prolonged iv infusion or by a series of daily injections. On the other hand, a single iv or ip injection of liposome-entrapped ARA-C has been shown to inhibit growth of iv and ip inoculated L1210 mouse leukemia. In the present study, the therapeutic efficacy of infused free and liposome-entrapped ARA-C was compared in DBA2/J mice bearing ip L1210 tumor. Dipalmitoylphosphatidylcholine:cholesterol 1:1 M ratio, reverse phase evaporation liposomes extruded through 0.4 micrometer nucleopore filters were used. These liposomes can be stored under nitrogen for 1 yr or more at 4 C in phosphate buffer and retain their antitumor activity. The half-life (T1/2; time for 50% ARA-C to leak out of the liposomes) was greater than 1 yr at 4 C and in the presence of 80% serum at 37 C the T1/2 was greater than 5 days. The av survival time (AST) of control mice injected ip with 10(6) L1210 cells was 7.8 +-0.7 days with 0/28 long term (30 day) survivors (LTS). The maximally effective dose of free ARA-C infused iv for 5 days into mice injected ip with 10(6) L1210 cells was 2.0 mg/kg/day. These mice survived 11.6 +-4.1 days with 0/18 LTS. A single iv injection of ARA-C entrapped in liposomes (10 mg/kg) 24 hr after injection of 10(6)6 L1210 cells ip resulted in an AST (mice dying before 30 days) of 10.9 +-6.6 days with a variable number of LTS (0/10, 1/8, 5/8, 7/8), total 13/34 in 4 separate experiments. The results indicate that a single injection of ARA-C entrapped in stable liposomes is as effective in terms of AST and may increase LTS compared to prolonged infusion of free drug in L1210 tumor. (no Refs)

220. INHIBITION OF TUMOR CELL GROWTH IN VITRO AND IN VIVO BY 1-BETA-D-ARABINOFURANOSYLCYTOSINE ENTRAPPED WITHIN PHOSPHOLIPID VESICLES.

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Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263.
Cancer Res; 36(12):4406-4411 1976

Phospholipid vesicles have been used as a carrier vehicle to enhance the cytotoxic activity of 1-beta-D-arabinofuranosylcytosine (ara-C) and 1-beta-D-arabinofuranosylcytosine 5'-triphosphate against several tumor cell lines. The activity of both compounds in free solution or entrapped within phospholipid vesicles was compared against L1210 cells, Ehrlich ascites cells, and SV40-transformed 3T3 cells in vitro. In addition, the activity of vesicle-entrapped ara-C against L1210 cells was also studied in vivo. The results obtained in vitro with ara-C indicated no difference in the concentration needed to inhibit growth of cells by 50% between free ara-C and vesicle-entrapped ara-C. In contrast, 1-beta-D-arabinofuranosylcytosine 5'-triphosphate entrapped in phospholipid vesicles was a more potent inhibitor of L1210 in culture (ID50, 2 x 10(-8) M) compared to the relatively inactive free 1-beta-D-

arabinofuranosylcytosine 5'-triphosphate (ID50, greater than 10(-7) M). Experiments carried out with L1210 cells in mice showed that, after a single ip dose (10 mg/kg) of vesicle-entrapped ara-C, the average survival times of mice inoculated with 10(5) L1210 cells were increased by over 90%. In control experiments, free ara-C or vesicles plus free ara-C (10 mg/kg) did not prolong survival of mice. (Author Abstract)

221. ENHANCEMENT OF THE CANCER CHEMOTHERAPEUTIC EFFECT OF CYTOSINE ARABINOSIDE ENTRAPPED IN LIPOSOMES ON MOUSE LEUKEMIA L-1210.

Kobayashi T, Tsukagoshi S, Sakurai Y
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Gann; 66(6):719-720 1975

Twenty-four hr after inoculation of CDF1 mice with 10(5) leukemia L-1210 cells, ip, varying doses of aqueous cytosine arabinoside (ara-C) or ara-C entrapped in liposomes were injected, ip. Doses of 50 or 100 mg of the aqueous soln had no significant effect on the ILS of the tumor-bearing mice although increased doses had a slight effect. A single dose of 50 mg/kg of the liposome entrapped ara-C markedly increased survival time, with 3/5 long-term survivors. Even with a low dose of 3.1 or 6.3 mg/kg, the effect was comparable to, or better than, that with 1,600 mg/kg of the aqueous ara-C. The admixture of the aqueous ara-C and drug-free liposomes did not result in ILS of tumor-bearing mice. (2 refs)

222. ENHANCEMENT OF ANTI-TUMOR ACTIVITY OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE BY ENCAPSULATION IN LIPOSOMES.

Kobayashi T, Kataoka T, Tsukagoshi S, Sakurai Y
Div. Experimental Chemotherapy, Cancer Chemotherapy Center, Japanese Foundation Cancer Res., Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Int J Cancer; 20(4):581-587 1977

Cytosine arabinoside (ara-C) was encapsulated in four different types of unsonicated artificial vesicles of phospholipid (liposomes) to compare the antitumor effect on mouse leukemia L1210 in CD2F1 mice with that of free ara-C. The antitumor activity of ara-C was markedly enhanced by encapsulation in liposomes when it was given in a single ip injection. A physically stable and positively charged liposome consisting of sphingomyelin, stearylamine, and cholesterol (20:2:15 molar ratio) enhanced the effect of ara-C most effectively. A single ip dose of 50 mg/kg of ara-C encapsulated in this liposome resulted in survival of 3/5 mice at 60 days, with the ratio of the mean survival time of treated mice to that of control mice (T/C) being greater than 381%, compared with a T/C of 114% for mice receiving 50 mg/kg of free ara-C ip. Ip administration of encapsulated ara-C prolonged the survival of mice inoculated with L1210 to a greater extent than free ara-C, regardless of whether single or multiple doses were given. An enhanced antitumor effect was also noted for encapsulated ara-C injected iv or sc. Max T/C values of 284% and 242% were observed when ara-C was encapsulated in the above liposome and injected sc at a dose of 100 mg/kg or iv at a dose of 50 mg/kg, respectively. The range between the minimum effective and max tolerable doses was wide enough to allow the safe use of encapsulated ara-C. (20 Refs)

223. FUNDAMENTAL APPROACHES TO THE CHEMOTHERAPY OF LYMPH NODE METASTASIS.

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Gann Monogr Cancer Res; (20):183-193 1977

An experimental metastatic tumor system involving the sc inoculation of CDF1 mice with 10(6) L1210 cells at the inner side of the right thigh was used to assess the effectiveness of various antitumor agents in preventing metastasis produced mainly in the retroperitoneal, inguinal, and axillary lymph nodes. When either of two alkylating agents (NSC-84641 and NSC-102627), both methanesulfonic acid esters of aminoglycol, was administered ip, sc, or iv 1 day after tumor inoculation for 4 consecutive days at doses of 20-30 mg/kg/day, a prolongation of survival time and an inhibition in lymph node size were observed compared with untreated controls. The iv route was the most effective. In other experiments, the number of L1210 cells proliferating in the lumbar lymph node was determined from a calibration curve by bioassay of the whole lymph node from CDF1 mice after sc inoculation of 10(6) L1210 cells. Chemotherapy with various agents was started 2 days after tumor inoculation. Single ip or iv injections of cytosine arabinoside (ara-C), daunorubicin, or 5-fluorouracil were ineffective in eradicating tumor cells in the lumbar lymph node even at doses of 1,600 mg/kg, 15 mg/kg, and 100 mg/kg, respectively. However, when a similar experiment was performed with *ara-C entrapped in liposomes* consisting of sphingomyelin, cholesterol, and stearylamine, no tumor cells were found in the lumbar lymph node 4 days after a single ip injection of 50 mg/kg of entrapped ara-C. Moreover, the effect of liposome-entrapped ara-C, even at doses of 3.1 or 6.3 mg/kg, was comparable to or better than that observed with 1,600 mg/kg of aqueous ara-C.

224. LIPOSOMAL ENHANCED ARAC CHEMOTHERAPY OF L-1210 IN BDF1 MICE. (MEETING ABSTRACT).

Griffin MJ, Lucid S
Ok Medical Res Fndn., Oklahoma City, OK 73104.
Proc Am Assoc Cancer Res; 18:183 1977

Liposomes form when water insoluble polar lipids, such as phospholipids, are homogenized with aqueous solutions. Such vesicles can improve chemotherapy by encapsulating the drug during formation resulting in improved drug stability and, when properly designed, may selectively seek out the tumor cell and aid in drug trans-membrane transport. Liposomes were prepared from sphingomyelin, cholesterol and stearylamine hydrochloride (7:2:0.2) by vortex mixing or sonicating the lipid mixture with saline containing various concentrations of AraC. BDF1 mice were injected IP with 10 highly syngeneic L-1210 cells and treated with various concentrations of free and liposome encapsulated AraC (Lip-AraC) one day later. The free drug at near maximum non-lethal dose (1250 mg/kg) gave a MST = 14.8 plus or minus 1.6 d, whereas Lip-AraC (75 mg/kg) gave a MST = 25.5 plus or minus 1.2 d (tumor controls MST = 10.0 plus or minus 0.3 d). Lip-AraC (50 mg/kg) was not toxic in non-tumor bearing mice, nor did liposomes alone have any therapeutic effect. By using four successive doses, at daily intervals, of hand-mixed Lip-AraC (12.5 mg/kg), 93% mice survived 30 days. Sonication of liposomes which reduces their size, raises the plateau concentration of drug needed for therapy, but is just as effective as mechanically prepared liposomes. (Author Abstract)

225. LIPOSOMAL ENCAPSULATED ARAC: IN VIVO AND IN VITRO TOXICITY TO L-1210 CELLS (MEETING ABSTRACT).

Griffin MJ, Killion JJ
Oklahoma Medical Res. Foundation, Oklahoma City, OK 73104
In Vitro; 13(3):152-153 1977

Cytosine arabinoside (ara-C) dissolved in saline was encapsulated in liposomes composed of sphingomyelin, cholesterol, and stearylamine hydrochloride (2:3:0.6) and was used to kill L-1210 cells in vivo (BDF1 male mouse) and in vitro. Mild sonication (1.5 min on ice) of mechanically formed liposomes resulted in 10 +- 1% ara-C encapsulated for in vivo studies. A single liposome-ara-C dose of 7.5 mg/kg given to mice 1 day after receiving 10(5) L-1210 cells resulted in a median survival time of 25.5 +- 1.2 days as compared with 10.0 +- 0.3 days for tumor-bearing controls and 14.8 +- 1.6 days for free ara-C at a near max non-lethal dose of 1,250 mg/kg. Liposome-ara-C (2.5 mg/kg) given to tumor-bearing mice (10(5) L-1210 at day 1) for 4 successive days resulted in a 93% 30-day survival; however, severe gastrointestinal toxicity was observed in mice receiving four successive doses of liposome-ara-C at a concentration of 33 mg/kg. For in vitro studies, liposomes were sonicated much more extensively (30 min with ice-water cooling) to obtain particles small enough to allow for microscopic counting of L-1210 cells. This extensive sonication resulted in 5 +- 1% ara-C encapsulation. The results of in vitro dose-response studies are not reported. (no Refs)

226. ROLE OF CHOLESTEROL IN ENHANCING THE ANTITUMOR ACTIVITY OF 1-BETA-D ARABINOFURANOSYLCYTOSINE (ARA-C) ENTRAPPED IN REVERSE PHASE EVAPORATION VESICLES (REV) (MEETING ABSTRACT).

Mayhew E, Rustum YM, Szoka F, Papahadjopoulos D, Paigen K
Roswell Park Memorial Inst., Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 20:186 1979

A new type of liposome was used to examine the effect of increasing the M ratio of cholesterol/phospholipid on the vesicle stability and on the antitumor activity of encapsulated 1-beta-D-arabinofuranosylcytosine (ara-C) against L1210 leukemia. Mice were injected ip with 10(6) cells on day 0 and treated with either a single dose of ara-C containing liposomes (10 mg/kg), ara-C alone (100 mg/kg), or non-encapsulated ara-C (100 mg/kg) plus liposomes on day 1. The lipid composition of the vesicles was phosphatidylglycerol (PG) and phosphatidylcholine (PC) with varying amounts of cholesterol. The results indicate that the greater the M ratio of cholesterol in the liposomes, the greater the survival time of the animals. This increase in survival time is correlated with the decreased leakage of ara-C from the liposome in the presence of 80% serum. At a 1/1 M ratio of phospholipid/cholesterol, 5/34 mice were long-term survivors. Results are tabulated. (1 Ref)

227. CHOLESTEROL CONTENT OF LIPOSOMES INFLUENCES THE CHEMOTHERAPEUTIC ACTIVITY OF ENCAPSULATED ARA-C (MEETING ABSTRACT).

Ganapathi R, Krishan A, Wodinsky I, Zubrod CG, Lesko LJ
Comprehensive Cancer Center, Univ. Miami, Miami, FL, 33101
Proc Am Assoc Cancer Res; 20:220 1979

Encapsulation of cytosine arabinoside (Ara-C) in liposomes has been reported to improve its antitumor activity in vivo. In the present study, we have compared Ara-C in anionic multilamellar liposomes with different lecithin:cholesterol (L:C) ratios and as a soln in L1210 leukemic mice. Increase in life span (%ILS) of tumor bearing mice injected ip on day 1 with Ara-C in liposomes of varying L:C ratios are tabulated. %ILS of mice treated with single doses of Ara-C in liposomes was related to L:C ratio. Max ILS was obtained at a dose of 40 mg/kg of Ara-C in liposomes with a L:C ratio of 1:1. The effect of L:C ratio on %ILS was not pronounced in multiple dose schedules (every 4.5 hr x 3). Multiple doses (40 mg/kg) with L:C ratios of 1:1 and 1:0.5 were toxic resulting in 83% and 50% mortality respectively by day 7. The study demonstrates that the in vivo activity of Ara-C in liposomes may be dependent on cholesterol content which may in turn be related to drug efflux and pharmacokinetics. (no Refs)

228. TREATMENT OF TUMOR BEARING MICE WITH LIPOSOME CAPTURED CYCLOCYTIDINE (MEETING ABSTRACT).

Ibuka T, Sakai Y, Hozumi T
Dept. Chemotherapy, Tokyo Metropolitan Komagome Hosp., Honkomagome, Bunkyo-ku, Tokyo 113, Japan
Proceedings of the 37th Annual Meeting of the Japanese Cancer Association held in Tokyo, Japan, August, 1978. Japanese Cancer Association Tokyo, Japan, 283 pp., 1978.

In order to determine whether cyclocytidine-C (cyclo-C) captured in liposomes enhanced the effect of intermittent administrations of small doses to the same degree as serial administrations, the antitumor effect on mouse leukemia L-1210 was examined. Antitumor effect was judged by percent ILS. The life-prolonging effect of a single administration of 27 mg/kg of cyclo-C liposome was greater than that of 1000 mg/kg of cyclo-C soln, and corresponded to 8 serial administrations of 100 mg/kg. (no Refs)

229. ENCAPSULATION OF 8-AZAGUANINE IN SINGLE MULTIPLE COMPARTMENT LIPOSOMES.

Fendler JH, Romero A
Dept. Chemistry, Texas A and M Univ., College Station, TX 77843
Lif Sci; 18(12):1453-1458 1976

Factors influencing the entrapment and retainment of 8-azaguanine in single and multilayer liposomes were investigated. Labeled 8-azaguanine was used to determine percentages of drug incorporation into liposomes and extent of leakage. The extent of encapsulation of drug into positively charged single compartment liposomes containing synthetic dipalmitoyl-DL-a- phosphatidylcholine, cholesterol, and stearylamine (wt ratios of 6:2:1.4) and those containing egg yolk phosphatidylcholine ranged from 0.70 to 1.84%. Extent of encapsulation in single compartment liposomes depended on the concentration of 8-azaguanine and sonication time. In multicompartment liposomes, extent of encapsulation ranged from 3.62 to 5.41%, suggesting that these liposomes appear to be superior vehicles for drug delivery. However, they are less uniform, more difficult to alter functionally, less permeable, and pass through the bloodstream of rats faster than single compartment liposomes. After 20 hr of dialysis, leakage of the drug from single compartment liposomes ranged from 4.0 to 33.7%. At high concentration of the added drug it was possible to encapsulate 18 x 10**-9 picomole of the drug/liposome. Preliminary in vivo experiments which tested liposomes as drug carriers were also performed on female DBF/1 mice bearing leukemia L1210, but results were disappointing. Mice treated with single compartment liposome encapsulated drug (0.04 mg/mouse/day, ip) survived for 7.0 +- 0.6 days and gained 14.7 +- 7% in body wt, and those treated with multiple compartment liposome encapsulated drug (0.76 mg/mouse/day, ip) survived for 8.3 +- 0.5 days with a wt gain of 6.6 +- 8.2%, compared to survival of 6.7 +- 1.0 days and wt gain of 16.3 +- 7.5% for controls. Thus, although the encapsulated drug

was nontoxic, only marginal increase in survival rate was noted. (21 refs)

230. RELATIVE ENHANCEMENT BY VARIOUS LIPOSOMES OF BCNU EFFECTIVENESS AGAINST L-1210 LEUKEMIA IN VIVO.

Ritter C, Rutman RJ
Dept. Animal Biology, Sch. Veterinary Medicine, Univ. Pennsylvania, Philadelphia, PA, 19104
Res Commun Chem Pathol Pharmacol; 30(1):123-131 1980

When max effective dose (MED) of carmustine (BCNU) is injected together with liposomes into mice with L-1210 leukemia, the effectiveness of the drug is decreased. But when half the MED is injected with liposomes into such mice, survival is increased compared to mice injected with BCNU alone. Study of liposome composition on BCNU anti-leukemic effect revealed that negatively charged liposomes made of dioleylphosphatidyl choline plus phosphatidyl serine given with half the MED of BCNU increased both long-term survival and mean survival time. This enhancement was not produced with negatively charged liposomes made of dioleylphosphatidic acid alone or in liposomes in which phosphatidyl serine plus dioleylphosphatidic acid was diluted with the neutral phospholipid, dioleylphosphatidyl choline. (Author abstract) (13 Refs)

231. INHIBITORY EFFECT OF CIS-DIAMINO-DICHLOROPLATINUM INCORPORATED INTO LIPOSOMES ON THE LYMPHOGENIC METASTASES OF A TRANSPLANTED MURINE TUMOR.

Kaledin VI, Matienko NA, Budker VG, Nikolin VP, Gruntenko EV
Inst. Cytology and Genetics, Novosibirsk, USSR
Dokl Akad Nauk SSSR; 242(2):473-476 1978

The hypothesis that incorporation of soluble antitumor drugs into liposomes might result in their accumulation in the regional lymph nodes and thus enhance the efficacy of prophylaxis and treatment of lymphogenic metastases was tested. A/He mice with an orthoaminoazotoluene-induced hepatoma A transplanted into a hind limb were inoculated with a suspension of liposomes containing 20 ug/ml of cis-diaminodichloroplatinum (DDP: sc, 4 x) or a DDP soln (sc, 4 x). The day after the last injection the extremity with the primary tumor was amputated and the development of metastatic tumors in the popliteal lymph nodes was monitored by daily palpation. DDP did not inhibit the growth of primary tumors; a DDP soln also did not inhibit the growth and development of regional metastases (daily gain in metastatic tumor wt was 33.8 mg compared with 35.8 mg in controls, and duration of latent period metastatic development was 71 days compared with 67 days in controls). The use of DDP incorporated into liposomes provided significant antimetastatic effect (the av daily gain in metastatic growth was 15.6 mg, and duration of latent period was 96 days). (10 Refs)

232. TUMOUR REGRESSION WITH LIPOSOME-ENTRAPPED ASPARAGINASE: SOME IMMUNOLOGICAL ADVANTAGES.

Neerunjun ED, Gregoriadis G
Clinical Res. Centre, Watford Road, Harrow, Middlesex, HA1 3UJ, U.K.
Biochem Soc Trans; 4(1):133-134 1976

The use of liposomes to entrap L-asparaginase (L-A), as a means of eliminating the allergic reaction to L-A but retaining its tumoricidal effect, was investigated and found to be effective and safe. Erwinia asparaginase (12,000 U) was entrapped in liposomes composed of egg phosphatidylcholine, cholesterol, and phosphatidic acid (negatively charged) or stearylamine (positively charged). C3H mice were given 4 x 10 6C3HED lymphoma cells i.m. Seven to nine d later the mice were inj with saline, free enzyme, negative-liposome-entrapped enzyme, or positive liposome-entrapped enzyme into the tail vein, peritoneal cavity, hind leg, thigh or tumor directly. All mice given saline died in 17-34 d with large tumors. The tumors of mice given free enzyme disappeared 1-2 d after L-A treatment; the mice were tumor free several mo later and were considered cured. However, pre-immunized tumor-bearing mice inj with a therapeutic dose of free enzyme died of serum sickness. Negative liposome-entrapped L-A inj i.v, i.p, or i.m prolonged the lives of 30 mice to 37-40 d and cured 10 only in larger doses. This preparation cured 60% when inj into the tumor mass directly. Positive liposome-entrapped L-A had a 100% cure rate when given i.m or into the tumor directly. Pre-immunized tumor-bearing mice were free of allergic reaction when given entrapped L-A. The concn of asparagine was much decreased (and aspartic acid increased) in serum and in tumors when mice were given free as well as entrapped enzyme. (9 refs)

233. MEDICAL APPLICATIONS OF LIPOSOME-ENTRAPPED ENZYMES.

Gregoriadis G
Immobilized Enzymes. Mosbach K, ed. New York, Academic Press, Methods in Enzymology, vol. 19, 1976.

The use of liposomes as vehicles for enzyme administration in humans and animals is reviewed. In vivo tests demonstrated that L-aspariginase entrapped in negatively-charged liposomes can cure lymphosarcoma in mice. (23 refs)

234. A COMPARISON OF THE THERAPEUTIC EFFECTS OF FREE AND LIPOSOMALLY ENCAPSULATED VINCRISTINE IN LEUKEMIC MICE.

Layton D, Trouet A
Inst. Cellular Pathology, UCL 75.39, Avenue Hippocrate, 75, B-1200 Bruxelles, Belgium
Eur J Cancer; 16(7):945-950 1980

The neurological toxicity of the Vinca alkaloids restricts their use in cancer chemotherapy. In this study we investigated the potential of liposomal encapsulation of one of these drugs, vincristine (VCR), to reduce this toxicity and hence increase the utility of this class of antimitotic agents. Plasma clearance studies for iv administration to NMRI mice, indicated that VCR included in liposomes was removed more slowly from the plasma than was free VCR, and that while the liposomes were in the circulation most of the VCR remained associated with its liposomal carrier. Early therapeutic trials of vincristine in liposomes, given iv to DBA/2 mice previously inoculated with P388 leukemic cells, demonstrated that considerable toxicity was caused by the lipid composition of the carrier (phosphatidylcholine, cholesterol and stearylamine). This toxicity was confirmed in in vitro screening of empty liposomes of various composition, and from this study a liposome composition of very low toxicity was selected (phosphatidylcholine, cholesterol and phosphatidylserine). Further therapeutic trials with the drug entrapped in 'non-toxic' liposomes showed that liposomal encapsulation of Vinca alkaloids did not provide any advantage either in terms of reduced toxicity or in increased therapeutic index over the free drug for the treatment of lymphocytic leukemia. (Author abstract) (13 Refs)

235. DNA, LIPOSOMES, AND PROTEINS AS CARRIERS FOR ANTITUMORAL DRUGS.

Trouet A, Baurain R, Deprez-De Campeneere D, Layton D, Masquelier M
ICP, 75 avenue Hippocrate, B-1200 Brussels, Belgium
Recent Results Cancer Res; 75:229-235 1980

The use of DNA, liposomes, and polypeptides or proteins as possible carriers for antitumor drugs was investigated. Daunorubicin (DNR) and adriamycin (ADM) were used as complexes with high mol wt DNA. These complexes were easily prepared, but they have poor stability in the bloodstream. This type of complex is restricted to anthracyclines that possess a high spontaneous affinity for DNA. DNR and vincristine (VCR) were entrapped in different liposomes without chemotherapeutic advantage. An attempt was made to link DNR to bovine serum albumin (BSA) in a covalent and a reversible manner. When DNR was linked directly to BSA, no DNR could be liberated enzymatically. As the length of the peptide spacer arm increased from one to four amino acids, the release of active DNR in the presence of lysosomal enzymes was progressively enhanced. Of the three carrier types tested, DNA had the great advantage of simplicity in preparation and liposomes were the most disappointing. (7 Refs)

236. INHIBITORS OF MAMMALIAN DNA POLYMERASES: POSSIBLE CHEMOTHERAPEUTIC APPROACHES.

Loeb LA, Agarwal SS, Dube DK, Gopinathan KP, Travaglini EC, Seal G, Sirover MA
Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111
Pharmacol Ther Dent; 2(1):171-193 1977

Inhibitors of DNA polymerases include antibodies, chemicals binding with the enzyme, template primer analogs, substrate analogs, agents modifying the DNA template, zinc chelators, divalent metal cations, and compounds of uncertain action (nitrosoureas, phosphonoacetate and bleomycin). It is hoped that inhibitors can be designed for facilitated entry into the cell, perhaps by using *liposomes* as a vehicle, and preferential inhibition of particular cellular DNA polymerases in vivo. Such agents might be able to take advantage of slight differences between normal and malignant cells, preferentially abolishing DNA replication in tumor cells. (148 Refs)

VII. METHODS FOR IMPROVING LOCALIZATION OF LIPOSOME-ENCAPSULATED SUBSTANCES

A.

Selective localization of liposomal drug release by hyperthermia

237. TREATMENT OF SOLID L1210 MURINE TUMORS WITH LOCAL HYPERTHERMIA AND TEMPERATURE-SENSITIVE LIPOSOMES CONTAINING METHOTREXATE.

Weinstein JN, Magin RL, Cysyk RL, Zaharko DS
Lab. Theoretical Biology, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 40(5):1388-1395 1980

'Temperature-sensitive' liposomes containing 3H-radiolabeled methotrexate ([3H]MTX) were injected iv into mice with L1210 tumor implanted in each hind foot. The lipid was radiolabeled with [14C]dipalmitoyl phosphatidylcholine. Encapsulated [3H]MTX at a dose of 0.0058 mg/kg was cleared from the plasma more rapidly when one foot was heated to 42 C in a water bath than when neither foot was heated. Four hr after injection of liposomes, the heated tumors contained an av of 14 x as much [3H]MTX as did the unheated ones. A large dose (300 mg/kg) of free, unlabeled MTX effectively blocked incorporation of [3H]MTX but not of [14C]dipalmitoyl phosphatidylcholine into the tumors, indicating that the differences observed with heating did not simply represent liposomes sequestered in the extravascular space of the tumors. These findings suggest that the temperature-sensitive liposomes break down preferentially in the heated tumor. Some of the released drug is taken up into the tumor cells via the usual transport mechanisms for MTX, and the rest circulates in the bloodstream to be cleared into other tissues and finally from the body by liver and kidneys. The lipid continues to circulate longer partly in association with serum apolipoproteins. In chemotherapy studies with MTX (3 mg/kg), the major findings were these: (a) liposome-encapsulated MTX caused a greater delay in tumor growth than did an equivalent concentration of free MTX with or without heating; and (b) heating alone of the tumor to 42 C for 1 hr delayed tumor growth for about 0.7 day, whereas heating increased by about 2.8 days the growth delay observed with heat-sensitive liposomes containing MTX (3 mg/kg). The nonadditive effect (about 2.1 days) corresponds to an extra cell kill of 4-to 16-fold. (Author abstract) (40 Refs)

238. LIPOSOMES AND LOCAL HYPERTHERMIA: SELECTIVE DELIVERY OF METHOTREXATE TO HEATED TUMORS.

Weinstein JN, Magin RL, Yatvin MB, Zaharko DS
Lab. Theoretical Biology, NCI, NIH, Bethesda, MD, 20014
Science; 204(4389):188-191 1979

Methotrexate (MTX)-containing liposomes with liquid-crystalline phase transition temperatures (Tc) near the range obtainable by local hyperthermia were prepared using a 7:3 (wt/wt) mixture of dipalmitoyl phosphatidylcholine (Tc = 41 C) and distearoyl phosphatidylcholine (Tc = 54 C). Mice with established (75-400 mg) 6- to 9-day-old sc Lewis lung tumors were given free 3H-MTX (6 ug/kg) or 3H-MTX-liposomes (100 mg/kg of lipid), iv, with or without local hyperthermia (42 C) to the tumors. Heating the tumors did not affect the clearance of free MTX, which was largely eliminated from the blood by redistribution within 3 min. The time constants for clearance of liposome-MTX from the blood were 38 min in the absence of hyperthermia and 23 min when the tumor was heated. After 1 hr, more liposomal MTX was present in the serum than the blood cells. Tumor uptake of MTX was enhanced (3.4-3.6x at both 4 and 20 hr after iv injection) only when MTX was given in liposomal form and the tumor was heated both before (about 15 min) and after (1 hr) MTX injection. In rats with bilateral sc tumors (one heated, the other unheated) given free or liposome-MTX, MTX uptake was in-

creased only in the heated tumors after administration of liposome-MTX. If the tumor was heated and cooled before chemotherapy, MTX uptake was not enhanced. When free MTX (300 mg/kg) was given simultaneously with liposome-MTX, uptake was largely inhibited in heated and unheated tumors at the level of either membrane transport or enzyme binding. It was suggested that local hyperthermia leads to release of MTX from liposomes (with the aid of serum components) and that the released MTX enters the cell by normal transport mechanisms. A direct liposome-cell interaction, rendered temperature-dependent because of changes in the liposomes, local vascular barrier, and/or tumor cells could not be ruled out. (28 Refs)

239. SELECTIVE LOCALIZATION OF LIPOSOMAL ENCAPSULATED METHOTREXATE IN LOCALLY HEATED MURINE TUMORS (MEETING ABSTRACT).

Magin RL, Weinstein JN, Yatvin MB, Blumenthal R
NCI, NIH, Bethesda, MD, 20014
Proc Am Assoc Cancer Res; 20:280 1979

We have used microwave-induced local tumor hyperthermia (LTH) and specially formulated heat-labile liposomes to enhance accumulation of the drug methotrexate (MTX) in Lewis lung carcinomas (LLC) in mice. The microwave power (at 2,450 megaHertz) was regulated to maintain a constant temperature of 42.0 +/-0.1 C in the center of each heated tumor. Intra-tumor temperature variations were +/-0.5 C, and rectal temperatures were kept in the range of 35-37 C. The liposomes used in these studies were small sonicated vesicles of dipalmitoyl and distearoyl phosphatidylcholines (3:1 mole/mole) which are quite stable at 37 C but release most of their contents in serum at 42 C. Liposomes containing 3H-MTX were injected by tail vein into mice with sc LLC after the tumor's temperature was raised to 42 C. Whole blood, tumor, and other tissues were removed for analysis at various times following a 60 min heating period. The application of LTH doubled the rate at which liposome encapsulated 3H-MTX was cleared from the blood and enhanced accumulation in the heated tumors at 4 hr after injection an av of 4.3 x the unheated controls. No enhanced clearance or accumulation of free 3H-MTX was found with local hyperthermia. High pressure liquid chromatography showed that essentially all of the 3H counts in the tumors were intact MTX. A large proportion of the accumulated MTX remained in the tumor 20 hr following injection and its accumulation was blocked by competition with unlabeled free MTX. These findings suggest that the accumulated MTX was intracellular and bound to its target enzyme dihydrofolate reductase. (no Refs)

240. USE OF HYPERTHERMIA FOR SELECTIVE LOCALIZATION OF LIPOSOMAL METHOTREXATE IN TUMORS (MEETING ABSTRACT).

Weinstein JN, Magin RL, Zaharko DS, Yatvin MB, Blumenthal R
NCI, Bethesda, MD, 20014
Biophys J; 25(2,part2):291a 1979

Use of liposomes as pharmacological capsules has been limited by the inability to direct them selectively to particular cells or anatomical sites. We have taken a new approach to the problem based on the well-known propensity of liposomes to release small solutes at temperatures near the phase transition. Small sonicated vesicles of 3:1 (M) dipalmitoyl phosphatidylcholine (DPPC)-distearoyl phosphatidylcholine (DSPC) were found to leak carboxyfluorescein dye maximally in the range 42.5 to 44.5 C during temperature scans. The release process could be accelerated by increasing the scan rate, by substituting multilamellar for small unilamellar vesicles, and, most dramatically, by including serum components in the medium. In a model system in vitro, neomycin released from DPPC-DSPC vesicles near the transition temperature effectively inhibited protein synthesis and colony formation by Escherichia coli. When DPPC-DSPC liposomes containing 3H-methotrexate (3H-MTX) were injected iv in mice carrying sc Lewis lung tumors, local microwave heating of the tumors to 42 C doubled the rate at which MTX was cleared from the blood, suggesting a release of drug from the vesicles in that small fraction of blood passing through the heated area in each circulation. Heated tumors accumulated on av 4.3 times as much MTX as unheated control tumors in the same animals. Two findings indicated that the accumulated MTX was intracellular and bound to its target enzyme, dihydrofolate reductase: (i) a large proportion of the MTX remained in the tumor even after 20 hr, (ii) its accumulation was largely blocked by competition with unlabeled free MTX. High pressure liquid chromatography showed virtually all of the 3H counts in the tumors to be from intact MTX. (no Refs)

241. SELECTIVE DELIVERY BY HYPERTHERMIA OF LIPOSOME ENCAPSULATED CIS DICHLORODIAMMINE PLATINUM(II) AND TUMOR GROWTH DELAY (MEETING ABSTRACT).

Yatvin MB, Muhlensiepen H, Porschen W, Feinendegen LE
Institut fur Medizin, KFA, D-5170 Julich 1, W. Germany
Proc Am Assoc Cancer Res; 21:281 1980

In an attempt to optimize the chemotherapeutic treatment of a mouse tumor (Sarcoma -180), liposomes containing cis-dichlorodiammineplatinum (II) (PDD), having transition temperatures a few degrees higher than the rectal temperature of mice, were used in combination with local hyperthermia. The uptake of radioactive PDD by tumors heated for 1 hr at 42 C was 3-fold higher when the drug was encapsulated in liposomes than if administered as free drug. Uptake of liposomes administered radioactive platinum by liver was twice that obtained with free PDD, whereas kidney and spleen were unchanged. The effect of various combinations of hyperthermia, drug-containing liposomes and free PDD on tumor growth delay was also studied. Treatment with liposome encapsulated PDD plus local heating resulted in a dose-modifying factor (DMF) of 7 when compared with free drug and no hyperthermia. A comparison was made between free drug combined with local hyperthermia and treatment with PDD liposomes and heat, the DMF for growth delay of the latter was about 2.5. Thus, even though PDD could be specifically released from liposomes by heat and results in both a greater drug uptake and a delayed tumor growth, potential normal tissue toxicity problems still need to be resolved before clinical application of this combined modality. (no Refs)

242. DESIGN OF LIPOSOMES FOR ENHANCED LOCAL RELEASE OF DRUGS BY HYPERTHERMIA.

Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R
Radiobiology Res. Lab., Dept. Human Oncology, Univ. Wisconsin, Madison, WI, 53706
Science; 202(4374):1290-1293 1978

Liposomes can be designed to release an entrapped drug preferentially at temperatures attainable by mild local hyperthermia. In a test system in vitro, protein synthesis by Escherichia coli is inhibited and killing of the cells is enhanced by heating neomycin-containing liposomes to their phase transition temperature to maximize drug release. In the presence of serum the ratio of release at 44 C to that at 37 C can be made greater than 100:1, suggesting possible

applications in the treatment of tumors or local infection. (Author abstract) (36 Refs)

243. LIPOSOMES ENGINEERED TO SELECTIVELY RELEASE DRUGS BY HYPERTHERMIA (MEETING ABSTRACT).

Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R
Radiobiology Res. Lab., Univ. Wisconsin, Madison, WI

14th Annual Meeting of the European Society of Radiation Biology held in Julich, W. Germany, 9-13 October 1978 113 pp., 1978.

Liposomes are microscopic structures consisting of one lipid bilayer enclosing a single aqueous compartment (unilamellar vesicles) or a number of concentric bilayers enclosing an equal number of aqueous spaces (multilamellar vesicles). They have been studied as vehicles for delivery of pharmaceutical agents, but a major barrier to their use has been the difficulty of directing them to specific sites. There are at least four ways in which local hyperthermia might increase the therapeutic effectiveness of drug-containing liposomes, for example, in the treatment of neoplasms: (1) by promoting selective drug release at temperatures near that of the lipid phase transition of the liposomes; (2) by increasing endothelial permeability to particles, thereby enhancing accumulation of liposomes in the target tissues; (3) by increasing the permeability or susceptibility of target cells to the encapsulated drug; (4) by increasing local transfer of drug from vesicles to cells (by fusion or endocytosis). Small unilamellar vesicles containing neomycin were prepared from dipalmitoyl-phosphatidylcholine and distearoylphosphatidylcholine (3:1) and heated at various temperatures from 22 to 50 C. In Escherichia coli B/r cells exposed to vesicles heated at temperatures consistent with the liquid-crystalline phase transition of the vesicles, incorporation of 3H-leucine was inhibited and killing enhanced. The use of multilamellar vesicles, rapid temperature increase and serum all amplify release of vesicle content. These studies suggest that differential cell toxicities to drugs can be achieved within the temperature range realistically obtainable by hyperthermic techniques. (no Refs)

244. USE OF HYPERTI.ERMIA TO PROMOTE SELECTIVE LOCAL RELEASE OF DRUGS FROM LIPOSOMES.

Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R
No affiliation given

Proceedings of a Conference on Clinical Prospects for Hypoxic Cell Sensitizers and Hyperthermia, held in Madison, WI, September 30 to October 2, 1977. 363 pp., 1978.

The possibility of using hyperthermia to enhance the selective delivery to target areas of liposome-encapsulated drugs was investigated. The rates of release of 6-carboxyfluorescein from unilamellar liposomes prepared from dipalmitoylphosphatidylcholine (DPPC) or 25% distearoylphosphatidylcholine (DSPC) and 75% DPPC, measured by fluorescence quenching technique at temperatures ranging from 20 C to 50 C, were highest at 38 C and 44 C, respectively. The inhibition of labeled leucine incorporation into proteins of Escherichia coli incubated with unilamellar DPPC:DSPC (3:1) liposomes containing approx 0.33 mg of neomycin for 10 min at temperatures ranging from 23 C to 50 C, was highest in the 42-44 C range. These results suggest that hyperthermia might increase the therapeutic effectiveness of drug-containing liposomes by promoting selective drug release at temperatures near that of the lipid-phase transition of the liposomes. (21 Refs)

245. TAILORING LIPOSOME STRUCTURE.

Gregoriades G
MRC Clinical Res. Centre, Harrow, Middlesex, England

Nature (Lond); 283(5750):814-815 1980

Developments in the use of liposomes to transport drugs to specific sites within the body are discussed. In order to decrease toxicity to normal tissues, target areas such as tumors may be preheated by hyperthermia, since liposomes become leaky at the melting temperature of their phospholipid component. Liposomal drugs delivered systemically can be released near and concentrate selectively in the preheated target areas. (28 Refs)

B.

Immunologic targeting of liposomes

246. TARGETING OF LIPID VESICLES: SPECIFICITY OF CARBOHYDRATE RECEPTOR ANALOGUES FOR LEUKOCYTES IN MICE.

Mauk MR, Gamble RC, Baldeschwieler JD
Div. Chemistry and Chemical Engineering, California Inst. Technology, Pasadena, CA, 91125

Proc Natl Acad Sci USA; 77(8):4430-4434 1980

The presence of particular surface carbohydrate modifications is shown to affect dramatically the stability and tissue specificity of unilamellar distearoyl phosphatidylcholine vesicles in mice. Use of the gamma-ray probe 111In+++ permits analysis of tissue distributions by standard gamma counting techniques and determination of the structural integrity of the vesicles by perturbed angular correlation spectroscopy. Addition of a 6-aminomannose derivative of cholesterol to the lipid bilayer produces initial retention of high levels of intact vesicles in the lung after iv injection followed by concentration of intact vesicles in the liver and spleen. Vesicles bearing 6-aminosugar residues are found to concentrate in the axillary space in aggregates of polymorphonuclear WBC when administered sc. The in vivo stability of 6-aminomannose-labeled vesicles is substantially greater after iv or sc administration than that observed for any other system examined. The dose-response effects observed with surface modifications indicate that a particular receptor topography is important in the mechanism leading to transport and destruction of these vesicles. (Author abstract) (18 Refs)

247. ANTIBODY TARGETING OF LIPOSOMES: CELL SPECIFICITY OBTAINED BY CONJUGATION OF F(AB')2 TO VESICLE SURFACE.

Heath TD, Fraley RT, Papahadjopoulos D
Div. Biology, Chester Beatty Res. Inst., London, England

Science; 210(4469):539-541 1980

A method devised for conjugating liposomes with protein resulted in the binding of up to 200 ug of IgG per micromole of lipid. The coupling of antibody to human RBC F(ab')2 in vesicles (149 molecules per vesicle) by this method caused a 200-fold increase in the binding of vesicles to human RBC and resulted in about 80% of the vesicle lipid and contents being associated with cells. (Author abstract) (14 Refs)

248. TUMOR-ASSOCIATED GANGLIO-N-TRIOSYLCERAMIDE. TARGET FOR ANTIBODY-DEPENDENT, AVIDIN-MEDIATED DRUG KILLING OF TUMOR CELLS.

Urdal DL, Hakomori S
Program of Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Univ. Washington, Seattle, WA, 98104
J Biol Chem; 255(21):10509-10516 1980

The tumor-associated glycolipid, ganglio-N-triosylceramide (GalNAcbeta1 leads to 4Galbeta1 leads to 4Glcbeta1 leads to 1Cer; GgOse3Cer) was used as a target for antibody-conjugated drug killing of tumor cells. Because of antibody inactivation by drug conjugation, targeting systems have been developed in which administration of biotinyl-anti-glycolipid antibodies was followed by successive addition of: (a) avidin and biotinyl drug (eg, neocarzinostatin) (b) avidin and biotinyl phospholipid liposomes in which actinomycin D was encapsulated; and (c) drug encapsulated in liposomes covalently linked to avidin. Successful targeting and killing of tumor cells expressing ganglio-N-triosylceramide was observed in System a above. Liposome targeting was successful in Systems b and c but liposome-targeted killing of the tumor cells was not efficient. Anti-ganglio-N-triosylceramide antibodies were derivatized with biotin-N-hydroxysuccinimide with full retention of their antibody function including complement-dependent cytolytic activity. In both Systems a and b above, avidin was used to bridge biotin-substituted drugs or drug carriers to biotinyl antibody bound to cells. Targeting required the presence of biotin on both the antibody and the drug or drug liposomes. Absorption of biotinyl antibody with guinea pig RBC (which contain ganglio-N-trioceramide) abrogated targeting. Furthermore, ganglio-N-triosylceramide on the target cells was identified chemically as three glycolipid spots separated on thin layer chromatography. These were characterized as having the same carbohydrate but different ceramides. Biotinyl neocarzinostatin was synthesized with decreased biological activity, but it gained the capacity to be directed to cells with avidin. Biotinyl liposomes encapsulating actinomycin D were prepared from biotinylphosphatidylethanolamine, lecithin, and cholesterol. In System c above, avidin was covalently linked to liposomes prepared with sialyllactosylceramide by reductive amination after the gentle periodate oxidation of the liposomes. This technique provides a useful basis for the covalent coupling of liposomes to biologically active proteins in general. (Author abstract) (52 Refs)

249. HOMING OF LIPOSOMES TO TARGET CELLS.

Gregoriadis G, Neerunjun ED
Clinical Res. Center, Harrow, Middlesex HA1 3UJ, England
Biochem Biophys Res Commun; 65(2):537-544 1975

The possibility of homing liposomes to target cells was investigated. Liposomes were prepared which contained the antitumor drug bleomycin and associated with molecular probes such as immunoglobulin G, raised against a variety of cells, and desialylated fetuin, which binds to heptatic parenchymal cells. In vitro experiments with human fibroblasts, HeLA cells, and AKR-A cells and in vivo experiments with Sprague-Dawley rats suggest that such probes are capable of mediating selective cellular uptake of the associated liposomes and the entrapped drug. For instance, immunoglobulin G raised against human fibroblasts and HeLA cells could discriminate between the surfaces of the respective cells, and this discrimination extended to liposome-associated immunoglobulin G, which effected selective cell association of the liposomal carrier and its bleomycin content. Only 20.5% of labeled liposomal bleomycin taken up by c311s (HeLA) via cell-specific immunoglobulin G was bound to plasma membranes; the remainder, presumably interiorized through endocytosis, was recovered in the lysosome-rich particulate fraction. It is anticipated that homing liposomes may become important tools in the control of cell behavior.

250. HOMING OF LIPOSOMES TO TARGET CELLS.

Gregoriadis G
Clin. Res. Cent., Harrow, Middlesex, England
Biochem Soc Trans; 3(5):613-618 1975

A method for guiding liposome-entrapped agents to specific cells by protein with an affinity for these cells is described. Uptake of entrapped In-labeled bleomycin (with IgG immunoglobulin as the affinity protein) was increased in HeLa, AKR-A cells, and in human skin fibroblasts, compared to uptake of bleomycin alone. (20 refs)

251. FATE OF LIPOSOME-ASSOCIATED AGENT INJECTED INTO NORMAL AND TUMOUR-BEARING RODENTS. ATTEMPTS TO IMPROVE LOCALIZATION IN TUMOUR TISSUES.

Gregoriadis G, Neerunjun DE, Hunt R
Clinical Res. Centre, Watford Road, Harrow, Middlesex, England
Lif Sci; 21(3):357-369 1977

Liposomes containing In111-labeled bleomycin were injected iv into normal and tumor-bearing rodents and the fate of radioactivity followed. In111 levels in tissues retained their max values for up to 48 hr after treatment thereby enabling accurate estimations of tissue participation which with a variety of tumors (Meth 'A', 6C3HED, Lewis lung carcinoma and Novikoff hepatoma) in mice and rats was secondary to that of the liver and spleen. Reductions in the size of liposomes decreased liver and spleen participation and increased tumor and kidney involvement. Uptake by lungs, skeletal muscle and brain was also augmented albeit to a lesser extent. Incorporation of anti-Meth 'A' cell immunoglobulin (IgG) into the liposomal carrier led to a modest increase in the uptake of co-entrapped In111 by the Meth 'A' tumor implanted sc. Although at the same time, liposomal IgG reduced uptake by the kidney, it effected a dramatic increase in hepatic and splenic involvement. This could be prevented by the concurrent administration of excess 'empty' liposomes which, however, did not interfere with uptake by tumor tissue. (Author abstract) (38 Refs)

252. TARGETING OF ANTIBODY COATED LIPOSOMES TO TUMOR CELLS PRODUCING CARCINOEMBRYONIC ANTIGEN (MEETING ABSTRACT).

Sharkey RM, Goldenberg DM, Primus FJ
Univ. Kentucky Medical Center, Lexington, KY, 40506
Fed Proc; 38(3,part2):1089 1979

Small lipid vesicles consisting of dipalmitoylphosphatidylcholine, cholesterol, and gangliosides (M ratio 11:8:1) were prepared by sonication in the presence of 131I and then coated with affinity-purified goat anti-carcinoembryonic antigen immunoglobulin G (anti-CEA IgG) or normal goat IgG. Following the removal of free 131I and antibody, the liposomes were incubated with a CEA producing cell line (HLC-1) for 1 hr at 37 C. The HLC-1 cells showed a two-fold increase in the incorporation of anti-CEA IgG coated liposomes when compared to a non-CEA producing cell line (Hela). This increased incorporation was not due to the preferential uptake by HLC-1 cells of IgG coated liposomes since lipcsomes coated with normal goat IgG bound equally well to both HLC-1 and Hela. Liposomes treated with normal goat IgG or left un-

treated reacted similarly. Thus, antibodies against a human tumor-associated antigen can confer specificity on liposome-cell interaction, thereby supporting the potential role of antibody-liposomes as specific carriers of diagnostic and therapeutic agents to tumors. (no Refs)

253. BINDING OF ANTIGEN-BEARING FLUORESCENT LIPOSOMES TO THE MURINE MYELOMA TUMOR MOPC 315.

Leserman LD, Weinstein JN, Blumenthal R, Sharrow SO, Terry WD
Immunology Branch, NCI, NIH, Bethesda, MD, 20014
J Immunol; 122(2):585-591 1979

Small unilamellar lipid vesicles bearing the dinitrophenyl (DNP)-hapten on their surfaces and containing the water-soluble fluorescent dye carboxyfluorescein were formed by sonication. These vesicles were incubated with cells from the murine myeloma tumor MOPC 315, which secrete and also bear on the cell surface an immunoglobulin with affinity for the nitrophenyl hapten. At 0 C the cells bound an av of several thousand vesicles at saturation. This binding was specific for the nitrophenyl hapten on the vesicle since it was abolished by an excess of soluble nitrophenyl derivative, by omission of the hapten from the vesicle, or by substitution for MOPC 315 of a tumor lacking receptors for the nitrophenyl hapten. Specific binding of vesicles was greater when cells were incubated at 37 C. The study suggests that ligand-bearing vesicles can be a useful marker for cell surface immunoglobulin. However, in spite of the ability to 'target' vesicles to cell surface determinants, binding did not result in increased delivery of vesicle contents to the cytoplasm. (Author abstract) (20 Refs)

254. INTERACTION OF HAPTEN-BEARING FLUORESCENT LIPOSOMES WITH MURINE MYELOMA TUMORS AND OTHER CELLS (MEETING ABSTRACT).

Leserman LD, Weinstein JN, Blumenthal R, Sharrow S, Moore JJ, Terry WD
NCI, NIH, Bethesda, MD, 20014
J Supramol Struct; (3):261 1979

Cell-liposome interactions were studied with sonicated liposomes containing the water-soluble fluorophore carboxyfluorescein and the antimetabolite methotrexate. Liposome membrane phosphatidylethanolamine was substituted with the dinitrophenyl or phosphorylcholine hapten. When these liposomes were incubated with myeloma cells only those liposomes corresponding to the binding specificity of the surface immunoglobulin of the tumor became associated with the cells, as confirmed by fluorescence microscopy and flow microfluorometry. This binding was inhibitable by the appropriate soluble hapten. Measurements of the incorporation of 3H-deoxyuridine showed that myeloma cells were sensitive to free methotrexate but that encapsulation of the drug in liposomes markedly reduced the drug effect whether or not cells bore the appropriate surface immunoglobulin. Specifically bound liposomes did not deliver methotrexate to the cytoplasm because they were not internalized by myeloma cells. Methotrexate encapsulated in hapten-bearing liposomes was more effective than free drug only when the liposomes were opsonized by exogenous anti-hapten antibody and presented to (non-myeloma) cell lines capable of endocytosing the liposomes. These studies illustrate the use of liposomes as stable markers of specific lymphoid cell surface receptors. (no Refs)

VIII. USE OF LIPOSOMES TO STUDY THE IMMUNE SYSTEM

A.

Use of liposomes to study macrophage tumoricidal properties in vivo and in vitro

255. TOXICITY STUDIES OF LIPOSOME-ENCAPSULATED IMMUNOMODULATORS ADMINISTERED INTRAVENOUSLY TO DOGS AND MICE.

Hart IR, Fogler WE, Poste G, Fidler IJ
Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
Cancer Immunol Immunother; 10(2/3):157-166 1981

The effects of single and multiple iv injections of large doses of liposome-encapsulated xenogeneic lymphokines were investigated in BALB/c or (C57BL/6 x C3H)F1 mice and in Beagles. Single injections of 2, 10, or 20 umoles of multilamellar vesicles (MLVs) containing encapsulated phosphate-buffered saline were given to Group I, six injections of 4 umoles of MLVs containing encapsulated supernatants from either normal lymphoyctes (NRSUPs) or mitogen-stimulated lymphocytes (MAFs) were given over a 6-wk period to Group II, and one injection/wk of 4 umoles of MLVs containing either NRSUPs or MAFs was given for 4 wk to Group III animals. The MLV liposomes were prepared from egg phosphatidylcholine, bovine brain phosphatidylserine, and egg lecithin. Clinical, hematologic, biochemical, immunologic, and histopathologic observations indicated that the liposome-encapsulated lymphokines were well tolerated by recipient animals, did not induce detectable toxicity or tissue changes, and could successfully activate mononuclear cell populations in specific anatomic compartments. (36 Refs)

256. THERAPY OF SPONTANEOUS METASTASES BY INTRAVENOUS INJECTIONS OF LIPOSOMES CONTAINING LYMPHOKINES.

Fidler IJ
Cancer Metastasis and Treatment Lab., Frederick Cancer Res. Center, Frederick, MD, 21701
Science; 208(4451):1469-1471 1980

Mice of two different strains were injected sc with spontaneously metastasizing syngeneic melanomas. After 4-6 wk, the local tumors were removed and, 3 days after surgery, treatment of the metastases was initiated. The treatment consisted of iv injections of liposomes containing lymphokines or control supernatant fluids. Liposomes were injected 2 x/wk for 3 wk, and the mice were killed 2 wk later. Seventy-three percent of the mice injected with liposomes containing lymphokines were free of metastases, whereas only 10% of the mice treated with control liposomes were tumor-free. These experiments suggest that this form of therapy may provide a valuable addition to the more conventional approaches to the eradication of cancer metastases. (Author abstract) (11 Refs)

257. IN SITU ACTIVATION OF MURINE MACROPHAGES BY LIPOSOMES CONTAINING LYMPHOKINES.

Fogler WE, Raz A, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, P. O. Box B, Frederick, MD, 21701
Cell Immunol; 53(1):214-219 1980

Murine alveolar and peritoneal macrophages harvested after injection of lymphokines encapsulated within multilamellar phospholipid vesicles (liposomes) were tumoricidal in vitro. The state and degree of activation depended on the route of liposome administration. Activation of peritoneal macrophages was achieved by ip injection of liposomes and alveolar macrophages were activated by injecting liposomes iv but not ip. The in vivo rendering of macrophages with tumoricidal properties might be useful toward destruction of tumor cells in vivo. (Author abstract) (17 Refs)

258. THE ROLE OF PLASMA MEMBRANE RECEPTORS AND THE KINETICS OF MACROPHAGE ACTIVATION BY LYMPHOKINES ENCAPSULATED IN LIPOSOMES.

Fidler IJ, Raz A, Fogler WE, Hoyer LC, Poste G
Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 41(2):495-504 1981

The kinetics of activation of tumoricidal functions in mouse macrophages incubated with macrophage-activating factors (MAF) released by mitogen-stimulated lymphocytes (free MAF) and MAF encapsulated within liposomes (liposome-MAF) have been compared. Development of tumoricidal activity requires incubation of macrophages with free or liposome-encapsulated MAF for a minimum of 4 hr. Macrophages incubated with MAF for 4 hr were not cytotoxic when tumor target cells were added immediately after removal of MAF, but they were highly cytotoxic when allowed to complete a 'lag' phase before being exposed to tumor cells. The duration of the lag phase varied with different activation protocols. The level of cytotoxic activity induced by liposome-encapsulated MAF was consistently higher than that obtained with free MAF. Studies using inhibitors of endocytosis demonstrated that internalization of the liposome carrier is required for activation by liposome-MAF and that activation does not result from MAF leaking from liposomes and binding to MAF receptors on either the plasma membrane or the membrane of endocytic vesicles. Comparison of the efficiency of macrophage activation by MAF encapsulated in liposomes of differing internal vol revealed that large multilamellar and large unioligolamellar liposomes were more efficient in activating peritoneal exudate macrophages than were small unilamellar liposomes. Measurement of the vol of liposome contents internalized by macrophages from these three types of liposomes revealed that max cytotoxicity required internalization of a given vol of MAF-containing lymphocyte supernatants, after which no further increase in cytotoxicity occurred. (Author abstract) (26 Refs)

259. IN VITRO ACTIVATION OF TUMORICIDAL PROPERTIES IN RAT ALVEOLAR MACROPHAGES BY SYNTHETIC MURAMYL DIPEPTIDE ENCAPSULATED IN LIPOSOMES.

Sone S, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Center, Frederick, MD, 21701
Cell Immunol; 57(1):42-50 1981

Alveolar macrophages (AM) lavaged from lungs of F344 rats were rendered tumoricidal by incubation in vitro with muramyl dipeptide (MDP). AM activated by this procedure were cytotoxic against syngeneic, allogeneic, and xenogeneic tumor cells but left cultures of normal (nontumorigenic) cells unharmed. MDP was encapsulated within multilamellar liposomes composed of phosphatidylserine-phosphatidylcholine. Dose-response experiments established that liposome-encapsulated MDP rendered AM tumoricidal at concentrations of approx 4,000x lower than free MDP present in the media. These data demonstrate that AM can respond in vitro to MDP and that MDP encapsulated within liposomes is more efficient in rendering AM tumoricidal than unencapsulated MDP. (Author abstract) (33 Refs)

260. DESIGN OF LIPOSOMES TO IMPROVE DELIVERY OF MACROPHAGE-AUGMENTING AGENTS TO ALVEOLAR MACROPHAGES.

Fidler IJ, Raz A, Fogler WE, Kirsh R, Bugelski P, Poste G
Cancer Metastasis and Treatment Lab., NCI Frederick Cancer Res. Center, Frederick, MD, 21701
Cancer Res; 40(12):4460-4466 1980

Factors affecting the localization of liposomes injected iv in the lung have been studied to identify the optimal type of liposome for delivery of macrophage-activating agents to the lung to augment the tumoricidal activity of alveolar macrophages (AM). Comparison of pulmonary retention of liposomes of differing size, surface charge, and composition following iv injection into inbred mice revealed that large multilamellar (MLV) and reversed-phase-evaporation (REV) liposomes are arrested in the lung more efficiently than are small unilamellar liposomes of identical lipid composition. MLV and REV containing negatively charged amphiphiles arrest in the lung more efficiently than do neutral MLV's or REV's or MULV's and REV's containing positively charged amphiphiles. Comparison of the ability of liposomes containing a variety of negatively charged amphiphiles to localize in the lung established that optimal localization was achieved using MLV and REV prepared from phosphatidylserine (PS) and phosphatidylcholine (PC) (3.7 mol ratio) or PS:PC:lysolecithin (4.95:4.95:0.1 mol ratio). The proportion of these liposomes retained in the lung after iv injection was constant over a wide dose range (0.02 to 20 umol phospholipid/mouse), but hemodilution due to iv inoculation of liposomes in vol exceeding in 0.2 ml reduced retention in the lung. Uptake of liposomes by AM was demonstrated by showing that iv injection of PS:PC MLV liposomes containing fluorescein-labeled bovine serum albumin resulted in localization of fluorescence within AM recovered by pulmonary lavage. Similarly, AM recovered after iv injection of PS:PC MLV liposomes containing lymphokine preparations rich in macrophage-activating factor (MAF) activity exhibited tumoricidal activity. In contrast, macrophages recovered from control animals given injections of unencapsulated MAF or liposomes containing lymphocyte supernatants without MAF activity were devoid of cytotoxic activity. Neutral (PC) MLV liposomes containing MAF, which show only very limited retention in the lung, were ineffective in activating AM in situ. We conclude that negatively charged MLV liposomes (PS:PC, 3:7 mol ratio) localize efficiently in the lung and that macrophage-activating agents encapsulated within such liposomes can successfully activate lung macrophages in situ. (Author abstract) (34 Refs)

261. SYNERGISTIC ACTIVATION BY LYMPHOKINES AND MURAMYL DIPEPTIDE OF TUMORICIDAL PROPERTIES IN RAT ALVEOLAR MACROPHAGES.
Sone S, Fidler IJ
(c/o Fidler) Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Center, Frederick, MD, 21701
J Immunol; 125(6):2454-2460 1980

Alveolar macrophages (AM) from lungs of normal F344 rats can be rendered tumoricidal by incubation in vitro with either muramyl dipeptide (MDP) at a minimum dose of 10 ug/ml or undiluted cell-free culture supernatants from mitogen-stimulated F344 rat lymphocytes rich in macrophage-activating factor (MAF) activity. Neither MAF at dilutions exceeding 1:6 nor MDP at doses lower than 10 ug/ml activated AM to become tumor cytotoxic. The combination of agents at subthreshold amounts (MAF 1:18; MDP 0.001 to 1 ug/ml) activated AM to significant levels of cytotoxicity. AM activated by these agents were rendered tumoricidal and destroyed syngeneic, allogeneic, and xenogeneic tumor targets in vitro. The synergism for AM activation between preparations of MAF and MDP required that AM be incubated first with MAF and then with MDP. Even a 15-min treatment of AM with MAF conditioned the cells to respond to subthreshold amounts of MDP and to be rendered tumoricidal. Since treatment of MAF and MDP with polymyxin B did not interfere with macrophage activation, we were able to rule out the possibility that our preparations were contaminated with lipopolysaccharide. Synergism for AM activation was demonstrated also when AM were treated with *MAF and MDP encapsulated within liposomes*. This finding suggests that the binding of agents to the macrophage surface is not a prerequisite for the synergistic activation of AM by MAP and MDP. (Author abstract) (42 Refs)

262. RAT ALVEOLAR MACROPHAGES ARE SUSCEPTIBLE TO ACTIVATION BY FREE AND LIPOSOME-ENCAPSULATED LYMPHOKINES.
Sone S, Poste G, Fidler IJ
Cancer Metastasis and Treatment Lab., NCI-Frederick Cancer Res. Center, Frederick, MD, 21701
J Immunol; 124(5):2197-2202 1980

Alveolar macrophages (AM) obtained from F344 rats were rendered tumoricidal by incubation in vitro with cell-free culture supernatant fluids rich in macrophage-activating factor (MAF) activity harvested from mitogen-stimulated F344 rat lymphocytes. AM activated by this procedure destroyed syngeneic, allogeneic, and xenogeneic tumor cells but were not cytotoxic for nonneoplastic cells. MAF was encapsulated in multilamellar lipid vesicles (liposomes) and its ability to render AM tumoricidal was compared with that of free (unencapsulated) MAF. Liposome-encapsulated MAF rendered AM cytotoxic at concentrations up to 16,000 x lower than free MAF. These data demonstrate that AM can respond in vitro to lymphokines and that MAF encapsulated within liposomes is far more efficient in rendering AM tumoricidal than free MAF. (Author abstract) (34 Refs)

263. ACTIVATION OF TUMORICIDAL PROPERTIES IN MOUSE MACROPHAGES BY LYMPHOKINES ENCAPSULATED IN LIPOSOMES.
Poste G, Kirsh R, Fogler WE, Fidler IJ
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 39(3):881-892 1979

Cell-free supernatants with high macrophage-activating factor (MAF) activity obtained from mitogen-stimulated F344 rat lymphocytes were encapsulated into liposomes of various sizes and lipid compositions. Normal macrophages from C57BL/6, C3H/Hen, or (C57BL/6 x C3H)F1 mice treated with encapsulated MAF exhibited significant cytotoxicity in vitro to syngeneic and allogeneic tumor cells (B16 melanoma, fibrosarcomas UV-112, and UV-2237, of C57BL/6, C57BL/6N, and C3H origin, respectively) but not to non-tumorigenic normal cells (TS normal epidermal cells of C3H origin or C57BL/6 mouse embryo cells). Liposome-encapsulated MAF rendered macrophages tumoricidal at concentrations at least 20,000x lower than free MAF. Since liposome-encapsulated MAF activated macrophages in the presence of a strong inhibitor of free MAF (p-nitrophenyl-2-O-alpha-L-fucopyranosyl- beta-D-galactopyranoside), it appears that encapsulated MAF was protected within the liposomes and that liposome-mediated activation was not caused by the release of small amounts of MAF into the medium by 'leaky' liposomes. Liposome-encapsulated MAF also activated macrophages which were refractory to activation by free MAF after either removal of presumably surface MAF receptors (by alpha-L-fucosidase and/or pronase) or occupation of the macrophages MAF receptor by fucose-binding plant lectins (Ulex europaeus or Lotus tetragonolobus agglutinins). Non-tumoricidal inflammatory tissue macrophages, inherently unresponsive to free MAF, became tumoricidal in vitro after incubation with liposome-encapsulated MAF. It is suggested that MAF can render macrophages tumoricidal by acting on intracellular sites. (57 Refs)

264. THE ROLE OF MACROPHAGE ACTIVATION IN HOST DEFENSE AGAINST NEOPLASIA.
Kirsh RL
State Univ. New York, Buffalo, NY
Diss Abstr Int [B]; 41(1):34 1980

Experiments were conducted to examine the nature of the macrophage-MAF (macrophage activation factor) interaction. The role of glycolipids as potential cell surface receptors for macrophage inhibitory factor (MIF) and MAF was examined. Incubation of culture supernatants from concanavalin A-stimulated guinea pig and rat lymphocytes with protein-free preparations of bovine brain gangliosides abolished their MIF and MAF activity. While the identity of the MIF/MAF-binding component(s) present in these glycolipid mixtures has yet to be established, absorption experiments with various purified mono-, di- and trisialogangliosides were negative. Since these gangliosides represent over 90% of the glycolipid content in brain ganglioside mixtures, it appears that the MIF-binding component(s) is present in only small amounts. Studies are detailed which show that normal macrophages from C57BL/6, C3H/Hen, and C57BL/6 x C3HF1 mice treated with *liposome-encapsulated MAF* exhibited significant in vitro cytotoxicity against syngeneic and allogeneic tumor cells but did not kill nontumorigenic normal cells. Dose-response measurements showed that liposome-encapsulated MAF was able to render macrophages tumoricidal at concentrations at least 20,000 x lower than free MAF. Studies with liposomes are reported which indicate that encapsulated MAF is protected within liposomes and that liposome-mediated activation was not caused by small amounts of MAF from 'leaky' liposomes. The ability of inflammatory tissue macrophages harvested on glass coverslips implanted in the sc tissue of C57BL/6 mice to kill tumor cells in vitro was examined. The alterations found in tumoricidal activity and responsiveness to lymphokines in vitro, are accompanied by a marked reduction in the number of peroxidase-positive macrophages, suggesting that maintenance of tumoricidal activity requires continuous

influx of new peroxidase-positive macrophages from the circulation. (no Refs)

265. CELL SURFACE RECEPTORS FOR LYMPHOKINES. I. THE POSSIBLE ROLE OF GLYCOLIPIDS AS RECEPTORS FOR MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) AND MACROPHAGE ACTIVATION FACTOR (MAF).

Poste G, Kirsh R, Fidler IJ
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cell Immunol; 44(1):71-88 1979

Incubation of culture supernatants from concanavalin A-stimulated guinea pig and rat lymphocytes with protein-free preparations of bovine brain gangliosides abolished their MIF and MAF activity. The identity of the MIF/MAF-binding component(s) present in these glycolipid mixtures has yet to be established, but adsorption experiments using purified preparations of mono- (GM1, GM2, and GM3), di- (GD1a), and trisialogangliosides (GT1) were negative. Since these gangliosides account for over 90% of the glycolipid content in brain ganglioside mixtures it appears that the MIF-binding component(s) is present only in very small amounts. Treatment of guinea pig peritoneal macrophages with *liposomes* containing similar brain gangliosides or water-soluble glycolipids extracted from guinea pig macrophages enhanced their responsiveness to MIF. The enhanced response to MIF of liposome-treated macrophages was abolished by incubation of the treated macrophages with fucose-binding lectins (Lotus agglutinin and Ulex europaeus agglutinin I) before exposure to MIF, suggesting that the MIF-binding component donated by the liposomes may be a fucose-containing glycolipid. The possible role of glycolipids as surface receptors for MIF and MAF is discussed. (Author abstract) (73 Refs)

266. RAPID DECAY OF TUMORICIDAL ACTIVITY AND LOSS OF RESPONSIVENESS TO LYMPHOKINES IN INFLAMMATORY MACROPHAGES.

Poste G, Kirsh R
Dept. Experimental Pathology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 39(7):2582-2590 1979

The ability of inflammatory tissue macrophages (harvested on glass coverslips implanted in the sc tissue of C57BL/6 mice) to kill tumor cells in vitro was examined. Macrophages present on coverslips implanted for 2 days lacked the ability to kill cultured syngeneic embryo cells and B16 melanoma cells. However, these macrophages could be rendered cytotoxic by incubation in vitro with lymphocyte culture supernatants containing macrophage activation factor. After this, they selectively killed B16 melanoma cells while leaving embryonic cells unharmed. Inflammatory macrophages recovered on coverslips implanted for 4-7 days exhibited selective cytotoxicity for B16 melanoma cells without the need for incubation in vitro with lymphokines. The tumoricidal activity of these macrophages was increased by further incubation in vitro with lymphokines. The cytotoxicity mediated by inflammatory macrophages activated in vivo and in vitro was selective for tumor cells. However, these macrophages killed both syngeneic and allogeneic tumor cells. Cytotoxic activity changed during the progression of the inflammatory reaction. Macrophages harvested on coverslips implanted for greater than or equal to 10 days were devoid of spontaneous cytotoxic activity and could not be rendered tumoricidal by incubation with lymphokines in vitro. These alterations were accompanied by a marked reduction in the number of peroxidase-positive macrophages within the population, suggesting that maintenance of tumoricidal activity requires continuous influx of new peroxidase-positive macrophages from the circulation. Previously activated macrophages that had lost their tumoricidal activity and had become refractory to reactivation by lymphokines in the extracellular environment could be reactivated by treatment in vitro with *liposomes containing encapsulated lymphokines*. (39 Refs)

267. MODIFICATION OF ANTITUMORAL CYTOTOXICITY OF MACROPHAGES BY LIPOSOMES AND ENDOTOXINS IN VITRO.

Olsson NO, Jeannin JF, Martin F
Laboratoire d'Immunologie, Faculte de Medecine, 7, boulevard Jeanne d'Arc, 21033 Dijon, France
C R Soc Biol (Paris); 174(6):1067-1071 1980

Liposomal modification of the cytotoxic effect of rat peritoneal macrophages on syngeneic colon cancer cells was studied. In cultures containing 10 mg of bacterial endotoxins, the cytolysis of cancer cells in the presence of macrophages activated by BCG was constantly increased when liposomes were added. The same liposomal effect was observed when the macrophages were not activated by BCG. In the absence of endotoxins, liposomes brought about a decrease of cytolysis. The amplifying effect of liposomes decreased when the concentration of endotoxins decreased from 20 to 1 mg/liter (l), disappeared at 0.1 mg/l, and had inverse effects at 0.01 mg/l. The importance of bacterial endotoxins in activating macrophages, cancer cells, and liposomes is stressed. (11 Refs)

268. ENHANCEMENT OF THE CHEMOTHERAPEUTIC POTENTIAL OF LIPOSOMES VIA MACROPHAGES BY ALKYL-LYSOPHOSPHOLIPIDS (MEETING ABSTRACT).

Luchenbach GA, Layton D, Andreesen R, Munder PG
Institut fur Tumorimmunologie, Max-Planck-Institut fur Immunbiologie, 78 Freiburg, W. Germany
Exp Hematol; 7(Suppl6):143 1979

We have shown that the coincubation of liposomes with L 1210 and L 929 cells can cause a wide range of effects on their viability. These effects are not particularly specific in terms of destroying the leukemic cells. However, we have observed that the combination of phosphorylcholine cholesterol (PC-Chol)-liposomes, which are not toxic by themselves with alkyl-lysophospholipids (ALP) as component of the liposome, can produce the desired specific cytotoxicity for leukemic cells. Here we report experiments, which show that the cytotoxic effect of vinca-alkaloids entrapped in PC-Chol-liposomes was enhanced by syngeneic mouse bone marrow macrophages by a factor 10. Activation of macrophages by the PC-Chol-liposomes could be ruled out as cause of the observed leukemic cell destruction. However, ALPs, which are known to be potent macrophage activators could be shown to be more effective in the liposomal form than in the free form. If vinca-alkaloids were entrapped in these macrophage activating liposomes, an at least additive effect of both macrophage attack as well as vinca alkaloid toxicity could be measured. We think the macrophage could act as a carrier for liposome entrapped drug and in addition as a means to target the selective drug delivery. On the other hand, liposomes partly composed of macrophage activating ALP and loaded with chemotherapeutic drug seems to be an ideal carrier of two effector mechanisms for attacking leukemic cells which might act synergistically. (2 Refs)

269. THE MURINE MACROPHAGE FC RECEPTOR FOR IGG2B IS LIPID DEPENDENT.
Anderson CL
Dept. Medicine, Univ. Rochester, Rochester, NY, 14642
J Immunol; 125(2):538-540 1980

The plasma membrane Fc receptor for IgG2b on P388D1 cells, solubilized by detergent, was inactivated by incubation with phospholipase C. Soluble Fc receptor activity could be restored by the addition of *liposomes* of either phosphatidylethanolamine or phosphatidylinositol. The reconstituted Fc receptor was trypsin sensitive. These data indicate that Fc receptor binding of IgG2b results from the concerted action of membrane lipid and protein. (Author abstract) (17 Refs)

270. A CYTOTOXIC FACTOR FROM MACROPHAGE MEMBRANES (MEETING ABSTRACT).
Zacharchuk CM, Drysdale BE, Shin M, Shin H
Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Fed Proc; 38(3,part2):1343 1979

Frozen-thawed or heat-killed macrophages have been shown to suppress tumor growth in vivo in the presence of antibody. In vitro, mouse macrophage membrane vesicles, prepared by vesiculation or sonication, inhibited tumor cell division as measured by 125IUdR uptake or cell count. Vesicles prepared from mouse 6C3HED tumor cells were not cytotoxic. Macrophage membranes were solubilized in 1% sodium dodecylsulfate (SDS) and chromatographed on a Sephadex G-100 column equilibrated with 1% SDS. After extensive dialysis, cytotoxicity was found in fractions eluting with an apparent mol wt of 30,000 daltons. Using 35S-SDS, it was determined that the amount of detergent remaining in the active fractions could not account for the cytotoxicity. The macrophage vesicles and the membrane fractions active in tumor cytotoxicity were also able to release 86Rb+ from *liposomes* made with dimyristoyl lecithin and cholesterol or from tumor cell targets. We conclude that macrophages have associated with their membranes a factor(s) which is cytotoxic for tumor cells and is capable of releasing 86Rb+ by damaging the lipid bilayer of liposomes and possibly tumor cells. (1 Ref)

B.
Use of liposomes to study immunity to tumors and tumor viruses in vivo

271. LIPOSOMES AS IMMUNOLOGICAL ADJUVANTS.
Allison AC, Gregoriadis G
No affiliation given
Recent Results Cancer Res; 56:58-64 1976

Liposomes, which are concentric spheres of lipid bilayers separated by aqueous compartments, appear to fulfill the requirement for an adjuvant system composed of biodegradable materials which does not provoke granulomatous reactions. Liposomes may also be useful as carriers of materials that increase the capacity of macrophages to kill tumor cells or inhibit their multiplication. Preparation of liposomes is straightforward and not much more time-consuming than preparation of conventional adjuvants. Diphtheria toxoid administered in negatively charged liposomes (iv) elicits formation of much higher concentrations of antibodies than are elicited by free antigen. Footpad inoculation (sc) of diphtheria toxoid in negatively charged liposomes elicits significantly higher antibody responses than the free antigen, although antigen in positively charged liposomes elicits less antibody than the free antigen. Mice immunized with diphtheria toxoid in liposomes challenged by footpad injection of the toxoid showed Arthus reactions at 6 hr, but no delayed hypersensitivity reactions at 24-72 hr. Immune mice inoculated with antigen-entrapped liposomes (sc or iv) did not develop serum-sickness reactions, whereas immune mice inoculated with free antigen (iv) developed severe serum-sickness and the majority died. The addition of saponin to liposomes with entrapped diphtheria toxoid further increases the antibody response to the toxin. No granulomas are formed at liposome injection sites, unlike injection sites of conventional adjuvants. These results indicate that liposomes are nontoxic, that they are not immunogeneic themselves, and that good immunostimulation may be achieved without any adverse effect on the patients. (8 refs)

272. LIPOSOMES AS IMMUNOLOGICAL ADJUVANTS.
Allison AC, Gregoriadis G
Lymphocytes, Macrophages, and Cancer. Mathe G, Florentin I, Simmler MC, ed. New York, Springer-Verlag, 1976.

Experiments involving the use of liposomes as immunological adjuvants are reported. Primary and secondary antibody responses in mice immunized with free and liposome-entrapped diphtheria toxoid (DT) (20 ug) were measured by indirect hemagglutination (IH) and were expressed as the log2 IH titer. DT administered iv in negatively charged liposomes to TO strain mice elicited the formation of much higher concentrations of antibodies than were elicited by the same dose of free antigen; the respective primary antibody responses were 10.0 and 1.8. Inoculation (sc) of DT in negatively charged liposomes elicited significantly higher primary and secondary antibody responses in CBA mice (6.7 and 13.3, respectively) than the same dose of free antigen elicited (2.5 and 11.6, respectively). In contrast, antigen entrapped in positively charged liposomes elicited less primary (0) and secondary (11.3) antibody responses than the same dose of free antigen. Im injection of DT in negatively charged liposomes again elicited significantly higher primary (3.7) and secondary (11.0) antibody responses in TO mice than were observed in mice receiving free DT (1.7 and 7.5, respectively). When protein antigens were administered together with heat-killed BCG or Bordetella pertussis to VSBS/NIMR mice, increased antibody responses and delayed hypersensitivity were observed. The primary and secondary antibody responses of mice infected im with DT entrapped in negatively charged liposomes that were admixed with BCG were 7.2 and 17.4, respectively, as compared with 0 and 12.6, respectively, for mice receiving free DT, O and 14.4, respectively, for mice receiving free DT plus BCG, and 1.4 and 12.8, respectively, for mice receiving DT entrapped in negatively charged liposomes only. Similar results were observed when the same strain of mouse was inoculated with liposome-entrapped DT plus B pertussis. Antibody responses were also increased when liposome-entrapped DT was administered in the presence of saponin. The primary and secondary antibody responses of VSBS/NIMR mice inoculated with 50 g of saponin in addition to liposome-entrapped DT (20 ug) were 0 and 12.6, respectively, as compared with 0 and 5.4 for mice inoculated with free DT, 0 and 7.5, respectively, for mice inoculated with DT entrapped in negatively charged liposomes, 0 and 6.5, respectively, for mice inoculated with 3 g of saponin and DT entrapped in negatively charged liposomes. No granulomas were formed at the sites of injection of liposomes, unlike the reactions observed at the sites of injection of conventional adjuvants. (8 refs)

273. DIRECT AND LIPOSOME-MEDIATED INTRODUCTION OF A FLUORESCENT HAPTEN AND A HAPTEN-CONJUGATED PROTEIN INTO TUMOR CELL MEMBRANE, AND INDUCTION OF TUMOR-SPECIFIC TRANSPLANTATION IMMUNITY WITH THE HAPTEN-CONJUGATED TUMOR CELLS.

Hashimoto Y, Yamanoha B, Endoh H, Ishizuka T
Pharmaceutical Inst., Tohoku Univ., Aramaki, Sendai 980, Japan
Gan Monogr Cancer Res; 23:135-141 1979

A fluorescent 5-dimethylamino-1-naphthalenesulfonyl (dansyl) group was introduced into the cell membranes of mouse or rat tumor cells, either by direct reaction of the cells or by fusion of liposomes conjugated with a dansyl group or dansyl-bound protein. Incubation of the tumor cells with a saturated solution of dansyl chloride in aqueous cyclohepta-amylose complex (CDC: 84 ug/ml of dansyl chloride) introduced a dansyl group into the cell membranes without destroying the cells. In C57BL/6 mice, ip immunization with dansyl-conjugated syngeneic EL4 leukemia cells (1/20-1/80 dilution of saturated CDC solution containing 10(6) EL4 cells) protected 26/30 mice against a challenge of 10(6) viable EL4 cells; 15/26 mice were protected against a larger tumor inoculum (5 x 10(6) cells). Dansyl-conjugated Yoshida sarcoma (YS) cells induced transplantation immunity against YS in Donryu rats. Sera and spleen cells from mice immunized with dansyl-conjugated EL4 cells plus untreated EL4 cells were cytotoxic to dansyl-conjugated or untreated EL4 cells in the presence of complement, but not to dansyl-conjugated or untreated allogeneic RADA1 leukemia cells. Immunization with dansyl-conjugated EL4 alone did not render the serum or spleen cells cytotoxic to any of the test cells. A dansyl group or dansyl-bound bovine serum albumin (BSA) was introduced into the cell membranes of Meth-A mouse sarcoma cells by incubation with liposomes conjugated with dansyl chloride. Cell membrane uptake of the reagent was demonstrated by fluorescence microscopy and by complement-dependent lysis of the tumor cells with anti-dansyl or anti-BSA antibody. (14 Refs)

274. SPECIFIC GLYCOLIPID ANTIGEN(S) IN SV40-TRANSFORMED CELL MEMBRANES.

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Institut de Recherches Scientifiques sur le Cancer, B. P. No 8, 94800 Villejuif, France
Int J Cancer; 25(6):797-803 1980

A glycolipid extract was prepared from an SV40-transformed hamster cell line (EH-SV) according to the Folch partition procedure. The glycolipids from the aqueous layer were incorporated in liposomal membranes composed of lecithin/sphingomyelin/cholesterol (1:1:2 by wt). This liposomal preparation was inoculated in Syrian hamsters to raise immune sera. The sera were absorbed with trypsinized 'normal' hamster cells (EH-N) and tested on various cell lines by the indirect immunofluorescence technique. When used for staining living cells, the immune serum produced a distinct cell-surface fluorescence with SV40-transformed cell lines regardless of the cell origin (eg, rat or hamster). No reaction was observed with heterologous Py-transformed cell lines, spontaneously transformed cells, or sera from nonimmunized hamsters. When used for staining acetone-fixed cells, the antiglycolipid serum reacted specifically with a thermostable antigen in the nuclear envelope and the cytoplasm of SV40-transformed cells. The sera lack interfering SV40 T reactivity. The results indicate the presence of related SV40-specific glycolipid antigen(s) in the plasma membrane, the nuclear membrane and probably other endomembranes of SV40-transformed cells. (Author abstract) (18 Refs)

275. SV40 TUMOR REJECTION INDUCED BY VESICULAR STOMATITIS VIRUS BEARING SV40 TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN (SV40-TSTA). II. ASSOCIATION OF SV40-TSTA ACTIVITY WITH LIPOSOMES CONTAINING VSV GLYCOLIPIDS.

Huet C, Ansel S
Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800 Villejuif, France
Int J Cancer; 20(1):61-66 1977

Highly purified vesicular stomatitis virus (VSV) was obtained from VSV-infected, simian virus 40 (SV40)-transformed and normal hamster cell lines. A glycolipid extract was prepared from these VSV preparations according to the Folch partition procedure. These glycolipids were rendered immunogenic to Syrian hamsters when incorporated within liposomal membranes composed of lecithin/sphingomyelin/cholesterol (1/1/2 by wt). When the glycolipids were extracted from VSV grown on cell lines (TSV5-cl2 and EHSVi-cl1) that contained the SV40 tumor-specific transplantation antigen (SV40-TSTA), it was possible either to induce tumor rejection or at least to slow the growth of the tumor in Syrian hamsters challenged with TSV5-cl2 cells. No protection was obtained in animals treated with liposomes containing glycolipids extracted from purified VSV grown on SV40-TSTA-negative cells (EHB). The SV40-TSTA could be a glycolipid of the transformed cell membrane that is incorporated within the VSV envelope. (29 Refs)

276. HUMORAL AND CELLULAR IMMUNITY TO HEPATITIS B VIRUS-DERIVED ANTIGENS: COMPARATIVE ACTIVITY OF FREUND COMPLETE ADJUVANT, ALUM, AND LIPOSOMES.

Sanchez Y, Ionescu-Matiu I, Dreesman GR, Kramp W, Six HR, Hollinger FB, Melnick JL
Dept. Virology and Epidemiology, Baylor Coll. Medicine, Houston, TX, 77030
Infect Immun; 30(3):728-733 1980

Complete Freund adjuvant, aluminum gel, and liposomes were compared for their ability to enhance the immunogenicity of an intact 22-nm HBsAg particle vaccine and an HBsAg-derived polypeptide vaccine in guinea pigs. Both humoral and cell-mediated immune responses were evaluated. The greatest immune response was obtained with complete Freund adjuvant, regardless of the antigen preparation. Aluminum gel appeared to be a better adjuvant for 22-nm HBsAg particles, but the liposomes rendered polypeptide preparations more immunogenic. The possibility that various proportions were entrapped in aqueous compartments instead of being inserted into the lipid bilayers of liposomes might account for this difference. The development of both humoral and cellular immunity was dependent upon the use of an adjuvant, because aqueous preparations had poor immunogenicity. (Author abstract) (22 Refs)

277. INDUCTION OF ANTIBODY RESPONSE TO LIPOSOME-ASSOCIATED GROSS-VIRUS CELL-SURFACE ANTIGEN (GCSAA).

Gerlier D, Sakai F, Dore JF
Laboratoire d'Immunologie et de Cancerologie Experimentale, INSERM FRA 24 Centre Leon Berard, Lyon, France
Br J Cancer; 41(2):236-242 1980

The immunogenicity of a soluble fraction containing Gross-virus-associated cell-surface antigen (GCSAa) obtained from (C58NT)D lymphoma cells either by detergent (NP40) solubilization or by 3M KCl extraction, was studied in syngeneic W/Fu rats. Rats immunized by 2 sc injections of soluble

antigen or soluble antigen mixed with empty liposomes and emulsified in complete Freund's adjuvant (CFA) failed to produce significant levels of cytotoxic antibodies to GCSAa. On the other hand, rats similarly immunized by negatively charged liposomes containing NP40-solubilized GCSAa, and emulsified in CFA, developed high and persistent levels of cytotoxic antibodies, and their response could also be obtained in rats immunized with liposome-associated NP40-solubilized GCSAa, but without CFA. Rats immunized by comparable amounts of liposome-associated 3M KCl-extracted GCSAa developed only low levels of cytotoxic antibodies, and their response was of shorter duration. These results strongly suggest that inclusion into liposomes of a solubilized protein tumor-associated cell-surface antigen can provide an immunogen as potent as viable tumor cells in inducing an antibody response, and that the solubilization method may be critical. (Author abstract) (22 Refs)

278. SPECIFIC IMMUNIZATION WITH LIPOSOME-ENTRAPPED TUMOUR-ASSOCIATED ANTIGEN (MEETING ABSTRACT).

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Medical Oncology. Abstracts of the 4th Annual Meeting of the Medical Oncology Society and the Bi-annual Meeting of the Immunology and Immunotherapy Group, Nice, France, December 2-4, 1978. New York, Springer-Verlag, 29 pp., 1978.

We investigated whether inclusion of a purified cell surface tumor associated antigen into an artificial membrane structure could succeed in inducing an antibody response. Gross-cell surface antigen (GCSAa) was obtained and partially purified. GCSAa activity was entrapped into multilamellar liposomes. The yield of entrapment of proteins was 30-50%. Analysis of liposomes thus formed showed that 1) the specific activity of GCSAa, expressed on a protein basis, was not modified by entrapment, 2) 4-10% of entrapped GCSAa was available at the liposome surface, and 3) nearly 30% of GCSAa could be found in the interlamellar aqueous phase, with most of the antigen being firmly associated with lipids. Injection of 0.43 mg protein of liposome entrapped NP40 extracted antigen with complete Freund adjuvant (CFA) induced a high antibody response in syngeneic rats that could mimic the response obtained with viable cells, while injection of 0.9 mg protein of soluble antigenic extract with CFA induced only a minor antibody response. An intermediate level of antibody response was obtained when GCSAa sensitized liposomes were injected without CFA. However, the antibody response was low in all three groups when 3 M KCl extracted antigen was used. Thus, injection of liposome entrapped viral tumor cell surface antigen can induce a good antibody response either by an adjuvant effect of liposome or by a membrane surface presentation effect of the antigen or both. The method used to extract the antigen could be an important factor in the level of immune response induced by liposome entrapped antigen. (no Refs)

279. ANTIBODY RESPONSE EVOKED IN SYNGENEIC ANIMALS BY A CELL SURFACE TUMOR ANTIGEN INCLUDED INTO LIPOSOMES (MEETING ABSTRACT).

Gerlier D, Sakai F, Dore JF

Lyon, France

Abstracts of the 5th Meeting of the European Association for Cancer Research, held in Vienna, Austria, September 9-12, 1979. European Association for Cancer Research, Vienna, Austria, 83 pp., 1979.

Gross cell surface antigen (GCSAa) extracted from W/Fu (C58NT)D rat lymphoma cells by NP40 or 3M KCl solubilization was associated with lipids (dipalmitoylphosphatidylcholine, cholesterol and dicetylphosphate in molar ratios of 7:2:1), so as to form multilamellar liposomes. About 75% of the liposome associated GCSAa activity was firmly associated with lipids, 1.0-8.0% of the GCSAa activity being expressed at the liposome surface. No striking differences were observed in the association of NP40 or 3M KCl extracted GCSAa with liposomes. Syngeneic W/Fu rats were immunized by 2 sc injections of solubilized or liposome-associated GCSAa and tested for cytotoxic anti-GCSAa antibody production. Rats immunized with liposomes sensitized with NP40 extracted GCSAa (0.80 mg protein) and emulsified in complete Freund Adjuvant (CFA) developed a high and persistent antibody response. Omission of CFA resulted in a lower antibody response, while immunization with NP40 solubilized GCSAa in CFA (1.46 mg) only resulted in a weak antibody response. All groups of rats immunized with comparable amounts of 3M KCl solubilized GCSAa developed low levels of cytotoxic antibodies. These results strongly suggest that inclusion into liposomes of a cell surface antigen can provide an immunogen as potent as viable tumor cells, and that the solubilization method may be of critical importance. (no Refs)

280. EFFECTIVE SUBUNIT VACCINES AGAINST AN ENVELOPED ANIMAL VIRUS.

Morein B, Helenius A, Simons K, Pettersson R, Kaariainen L, Schirrmacher V

European Molecular Biology Lab., Heidelberg, W. Germany

Nature (Lond); 276(5689):715-718 1978

The preparation of effective vaccines against Semliki Forest virus (SFV) using the viral spike protein as the immunogen is reported. Three spike protein preparations were tested: the 4.5 Svedberg unit (S) complex, a complex of one spike protein bound to 75 molecules of Triton X-100 (monomer); the 29 S complex, a protein micelle of eight spikes virtually devoid of lipid and detergent with a mol wt of 9.4 x 10(5) (octamer); and *virosomes*, in which the spike proteins have been reconstituted into vesicles of egg lecithin (multimer). Mice were immunized with 10 ug spike protein in 100 ul Eagle's minimal essential medium, one-third sc and two-thirds ip. Mice were challenged 2 wk later with a virulent virus strain in doses ranging from 50 to 10(7) plaque-forming units. The LD50 was determined for each physical form of the vaccine: 2.7-3.4 for the 4.9 S complex, greater than 3.5 to greater than 6.3 for the 29 S complex, and greater than 4.0 to greater than 6.6 for the virosomes. The control LD50 was in the range of 2.1-2.6. Vaccination with the monomeric preparation of the spike protein gave a small but detectable protection against the disease, while vaccination with either of the other two preparations gave good protection. Experiments with nude mice showed, as previously reported, that T cells appeared to be required for the vaccination to give protective immunity. Results of previous studies

on the immunogenicity of spike protein preparations of other viruses are discussed. (36 Refs)

281. THE ISOLATION OF A CELLULAR HYBRID PRODUCING A SPECIFIC ANTIBODY OF HUMAN LEUKOCYTE INTERFERON.
Montagnier L, Laurent AG, Gruest J
Equipe de Recherche 147, C.N.R.S., 28, rue due Docteur-Roux, 75015 Paris, France
C R Acad Sci [D] (Paris); 291(11):893-896 1980

A study of the isolation of a cellular hybrid producing a specific antibody of human WBC interferon (IF) is reported. A mouse was immunized against *IF which was incorporated into liposomes.* Splenic lymphocytes from the mouse were fused with a nonsecreting variant of the myeloma P3X63 Ag8 which came from the MOPC-21 line. Of 842 cellular hybrids obtained and tested, a single one, called HBA, secreted a substance capable of neutralizing IF in a reproducible manner. The monoclonal antibody, IgG, also recognized human IF made by a bacterial recombinant and a fraction of IF made by Namalva cells. (13 Refs)

C.
Other in vitro immunologic studies utilizing liposomes

282. CELL-MEDIATED IMMUNITY TO HERPES SIMPLEX VIRUS: INDUCTION OF CYTOTOXIC T LYMPHOCYTE RESPONSES BY VIRAL ANTIGENS INCORPORATED INTO LIPOSOMES.
Lawman MJ, Naylor PT, Huang L, Courtney RJ, Rouse BT
(c/o Rouse) Coll. Veterinary Medicine, Dept. Microbiology, Univ. Tennessee, Knoxville, TN, 37916
J Immunol; 126(1):304-308 1981

The immunogenicity of inactivated herpes simplex virus type 1 (HSV-1) antigens incorporated into liposomes was measured by their ability to induce secondary anti-HSV-1 specific cytotoxic T lymphocyte (CTL) responses in splenocyte cultures from virus-primed mice. Such virus-specific CTL could be induced provided the liposomes contained virus along with plasma membrane antigen of the same H-2 type as that of the virus-primed responder cells. Responses did not occur in cultures stimulated with liposomes containing only viral antigens or with a mixture of liposomes composed respectively of lipid and virus with those composed of lipid and plasma membrane proteins. Moreover, F1 responder cells stimulated with liposomes composed of virus and plasma membrane protein of one of the parental haplotypes produced CTL restricted in their cytotoxicity to infected targets of the same haplotype as was used in the liposome. These results show that liposomes can be used to induce anti-HSV-1 CTL with inactivated viral antigens but recognition of both viral and H-2 antigen is required for this process to occur in vitro. The implications of our findings to the preparation of subunit vaccines against HSV-1 are briefly discussed. (Author abstract) (17 Refs)

283. CELLULAR INTERACTIONS IN THE GENERATION OF CYTOLYTIC T LYMPHOCYTE RESPONSES: ROLE OF IA-POSITIVE SPLENIC ADHERENCE CELLS IN PRESENTATION OF H-2 ANTIGEN.
Weinberger O, Herrmann SH, Mescher MF, Benacerraf B, Burakoff SJ
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
Proc Natl Acad Sci USA; 77(10,part2):6091-6095 1980

Splenic adherent cells are required for generation of both primary and, at limiting antigen dose, secondary allogeneic responses of cytolytic T lymphocytes to intact stimulator cells. Secondary responses to purified allogeneic plasma membranes or *purified H-2Kk antigens in liposomes* are also dependent upon splenic adherent cells. Generation of these responses requires the presence of an Ia-positive, Thy 1.2-negative, radiation-resistant cell in the splenic adherent cell population that is adherent to glass, plastic, and nylon wool. Stimulation of cytolytic T lymphocyte precursors with purified H-2Kk alloantigen bound to Ia+ splenic adherent cells is 10-20 times more efficient than stimulation with antigen added directly to culture. Furthermore, a marked decrease in the response of cytolytic T lymphocytes to liposomes was observed when antiserum against Iad specific for the Ia of the responder cells was added to culture. These results demonstrate that, for purified proteins of the major histocompatibility complex, antigen presentation by Ia+ splenic adherent cells plays a role in the generation of a cytolytic T lymphocyte response. (Author abstract) (23 Refs)

284. SPECIFICITY OF MOUSE CYTOTOXIC T LYMPHOCYTES STIMULATED WITH EITHER HLA-A AND -B OR HLA-DR ANTIGENS RECONSTITUTED INTO PHOSPHOLIPID VESICLES.
Engelhard VH, Kaufman JF, Strominger JL, Burakoff SJ
Biological Lab., Harvard Univ., Cambridge, MA, 02138
J Exp Med; 152(2,part2):54s-64s 1980

Distinct populations of murine cytolytic T lymphocytes (CTL) were derived from primed spleen cells using preparations of HLA-A and -B (HLA-AB) or HLA-DR antigens reconstituted into phospholipid vesicles, and the specificities of the CTL were studied. The HLA-DR liposomes induced killers (of Jy cell targets) with a max lytic activity significantly greater than that induced by an equal amount of HLA-AB liposomes. The lytic activity was dependent on the amount of antigen added and the effector:target ratio. The phenotypes of these CTL antigens were similar to those specific for class I histocompatibility antigens. Cytolysis by CTL stimulated by HLA-A2 or HLA-B7 liposomes could be blocked by anti-HLA-AB antisera but not by anti-HLA-DR antisera. The reverse pattern was seen with CTL stimulated by HLA-DR liposomes. When tested with a panel of target cells expressing various HLA-AB or HLA-DR allospecificities, the strongest CTL reactivity was directed toward cells bearing the same allospecificities as those on the liposomes. Target cells expressing cross-reactive or unrelated specificities were not recognized as well. The results suggest that, despite species differences, there was a strong conservation of histocompatibility antigen structure during evolution and that the region of the molecules that bears the xenoantigenic site is the same as, or spatially close to, that bearing the alloantigenic site. (32 Refs)

285. INDUCTION OF VIRUS-SPECIFIC, H-2 RESTRICTED MURINE CTL BY LIPOSOMES (MEETING ABSTRACT).
Mescher MF, Finberg R, Burakoff S
Dept. Pathology, Harvard Medical Sch., Boston, MA, 02115
J Supramol Struct; (3):259 1979

Liposomes containing Sendai virus membrane proteins and partially purified H-2d antigens are able to stimulate a virus specific, H-2 restricted secondary cytotoxic T lymphocyte (CTL) response. Liposomes were prepared by mixing deoxycholate-solubilized virus membrane proteins, lectin-purified H-2d antigens and phospholipid, followed by removal of the detergent by dialysis in the presence of calcium. When placed into culture with spleen cells from B6D2F1 (H-2b/H-2d) mice previously immunized with Sendai virus, these

liposomes stimulated the generation of a secondary CTL population specific for Sendai virus-coated P815 (H-2d) tumor cell targets. No lysis was found using Sendai-coated EL4 (H-2b) targets, thus demonstrating that the viral proteins are recognized in the context of the H-2 antigens present in the liposomes. Reciprocal results were obtained using liposomes containing viral proteins and H-2b antigens. Mixing experiments demonstrated that T cell recognition requires that both the viral proteins and the H-2 antigens be present in the same membrane. Thus, no CTL response is obtained if liposomes containing only viral proteins are added to cultures along with liposomes containing only H-2 antigens. The Sendai virus membrane proteins have now been purified by diethylaminoethyl chromatography in the presence of Triton X-100 and experiments are in progress to determine which of these proteins is required for CTL induction. (no Refs)

286. INDUCTION OF SECONDARY CYTOTOXIC T LYMPHOCYTES BY PURIFIED HLA-A AND HLA-B ANTIGENS RECONSTITUTED INTO PHOSPHOLIPID VESICLES.

Engelhard VH, Strominger JL, Mescher M, Burakoff S
Biological Lab., Harvard Univ., Cambridge, MA, 02138
Proc Natl Acad Sci USA; 75(11):5688-5691 1978

Mouse cytotoxic T lymphocytes were induced by culturing primed spleen cells with cells, membranes, or detergent-solubilized and dialyzed membranes from the human lymphoblastoid cell line JY. Cytotoxic T cells could also be induced by coculturing primed spleen cells with phospholipid vesicles containing purified human leukocyte antigen (HLA)-A and -B antigens derived from JY cells. The induction of killer cells by all subcellular fractions demonstrated an optimal response as a function of the amount of material added and, in the case of HLA-containing liposomes, this optimum was dependent upon the density of the HLA molecules in the liposomes. In addition, the maximal level of cytotoxicity elicited was also dependent upon this density. Finally, the cytotoxic cells demonstrated specificity as judged by a lower level of lysis on an HLA-unrelated lymphoblastoid cell line than on the appropriate target, JY. These results suggest that major histocompatibility antigens alone are sufficient for the induction of a secondary cytotoxic T lymphocyte response. It is proposed that this system may be useful in defining possible sites on the HLA molecule recognized by cytolytic T lymphocytes. (Author abstract) (23 Refs)

287. LIPOSOME-MEDIATED TRANSFER OF INTEGRAL MEMBRANE GLYCOPROTEINS INTO THE PLASMA MEMBRANE OF CULTURED CELLS.

Poste G, Lyon NO, Mecander P, Porter CW, Reeve P, Bachmeyer H
Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Exp Cell Res; 129(2):393-408 1980

Cultured BALB/c mouse 3T3 cells exposed to liposomes of phosphatidylcholine or phosphatidylserine:phosphatidylcholine (3:7 molar ratio) containing orthomyxovirus or paramyxovirus (Sendai, Newcastle disease, or influenza A) envelope glycoproteins became susceptible to killing by virus-specific cytotoxic BALB/c T-lymphocytes, indicating that the liposome-derived glycoproteins had been inserted into the cellular plasma membranes. When the cells were incubated with liposomes of similar lipid composition containing both viral antigens and a dinitrophenylated lipid hapten, they were susceptible to killing by both virus-specific and hapten-specific T-lymphocytes, showing that both protein and lipid components had been inserted into the plasma membrane. The assimilation of liposome-derived antigens into the plasma membrane was believed to be caused by the fusion of liposomes with the plasma membrane. Because cells incubated with phosphatidylcholine liposomes containing lipid haptens and viral glycoproteins were not killed by cytotoxic T-lymphocytes, liposomes of this composition apparently did not fuse with the plasma membrane. Liposome-derived paramyxovirus glycoproteins inserted into the plasma membranes retained their functional activities, as shown by their ability to induce cell fusion. It is concluded that liposomes can be used as carriers for introducing integral membrane (glyco) proteins into the plasma membranes of cultured cells. These experiments provide a new approach for studying the role of individual (glyco)proteins in the expression of specific cell surface properties. (62 Refs)

288. ANTIGEN-LIPOSOME MODIFICATION OF TARGET CELLS AS A METHOD TO ALTER THEIR SUSCEPTIBILITY TO LYSIS BY CYTOTOXIC T LYMPHOCYTES.

Hale AH, Ruebush MJ, Lyles DS, Harris DT
Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103
Proc Natl Acad Sci USA; 77(10,part2):6105-6108 1980

A method of liposome modification of cell surfaces to render unsuitable target cells susceptible to lysis by antiviral cytotoxic T lymphocytes (CTLs) is described. *Liposomes* containing the hemagglutinin-neuraminidase (HN) and fusion (F) glycoproteins of Sendai virus as well as purified H-2Kk antigens were capable of binding to the surface of H-2-negative cells and rendering those cells susceptible to lysis by B10-A anti-Sendai virus or anti-H-2Kk CTLs. The absence from the modifying liposomes of the HN or F proteins or H-2Kk antigens eliminated the ability of the target cells to be recognized and lysed by either effector cell population. Vesicles containing HN, H-2Kk molecules, and inactive fusion protein (Fo) were not capable of increasing the susceptibility of H-2-negative target cells to lysis. Liposomes containing inactive fusion protein were similarly unable to render H-2-positive target cells susceptible to lysis by anti-Sendai virus CTLs, suggesting that fusion of the liposomes to the cell surface is a prerequisite to lysis. It did not appear that attachment of liposomes to the cell surface was sufficient for generation of susceptible targets, however, because attachment to the cell surface was observed, as long as the HN glycoprotein was present in the liposomes. These results indicate that purified H-2Kk glycoproteins are target antigens for anti-H-2k CTLs and that B10-A anti-Sendai virus CTLs recognize in an H-2-restricted manner the HN, F, or both glycoproteins of Sendai virus in the context of the purified H-2Kk glycoproteins. This technique of liposome modification of cell surfaces has potential applications in the examination of CTL antigen recognition and immunotherapy of many viral and neoplastic diseases. (Author abstract) (19 Refs)

289. H-2 ANTIGENS INCORPORATED INTO PHOSPHOLIPID VESICLES ELICIT SPECIFIC ALLOGENEIC CYTOTOXIC T LYMPHOCYTES.

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Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103
Cell Immunol; 55(2):328-341 1980

Different H-2 antigen-containing subcellular fractions were tested for their ability to elicit specific anti-H-2 cytotoxic T

lymphocytes (CTLs). Intact cells and membrane vesicles were capable of eliciting strong anti-H-2 primary and secondary CTL responses. However, detergent-solubilized H-2 antigens partially purified with lentil lectin were greatly reduced in their capacity to elicit secondary anti-H-2 (CTLs) and at all amounts tested did not elicit a primary CTL response. Lentil lectin-purified H-2 antigens incorporated into egg lecithin plus cholesterol (30% wt/wt) vesicles elicited a strong secondary anti-H-2 CTL response and a low but significant primary anti-H-2 CTL response. The results also indicate that T-cell-defined specificities are closely associated with serologically defined private and public specificities. (Author abstract) (26 Refs)

290. ELICITATION OF ANTI-VIRAL CYTOTOXIC T LYMPHOCYTES WITH PURIFIED VIRAL AND H-2 ANTIGENS.

Hale AH, Ruebush MJ, Harris DT

Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Winston-Salem, NC, 27103

J Immunol; 125(1):428-430 1980

The minimal molecular requirements for elicitation of secondary anti-Sendai virus CTL were investigated. The hemagglutinin-neuraminidase (HN) glycoprotein of Sendai virus and the H-2Kk glycoprotein of YAC tumor cells were purified and incorporated into phospholipid vesicles. These unilamellar liposomes were then tested for the ability to elicit H-2 restricted secondary anti-Sendai virus CTL. The results indicate that these well-defined vesicles were capable of eliciting secondary anti-Sendai virus CTL which lysed only target cells possessing the H-2Kk haplotype and modified with inactivated Sendai virus. (Author abstract) (13 Refs)

291. MINIMAL MOLECULAR REQUIREMENTS FOR REACTIVITY OF TUMOR CELLS WITH T CELLS.

Hale AH, Lyles DS, Paulus LK, Ruebush MJ

Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC, 27103

J Immunol; 124(5):2063-2070 1980

We have investigated the minimal molecular requirements for T cell recognition of a previously described myeloma tumor (MOPC-315-EL), which reversibly alters its reactivity with T cells. Enucleation of MOPC-315 cells, either sensitive or resistant to reaction with T cells, did not alter the ability of the resulting cytoplasts to elicit or serve as targets for anti-H-2 or anti-Sendai viral cytotoxic T lymphocytes (CTL), despite the fact that there were no detectable differences in serologically defined H-2 or viral antigens on their surface. Likewise, when plasma membranes isolated from sensitive or resistant cells were tested for their ability to elicit anti-H-2 CTL, they retained the phenotype of the cells from which they were isolated. However, solubilized and partially purified H-2 antigens from both sensitive and resistant cells were able to elicit H-2-restricted anti-Sendai virus CTL when incorporated into *liposomes* with purified viral glycoproteins, and anti-H-2 CTL when incorporated alone into liposomes. These results suggest that a cellular surface component(s) exists that is probably not an H-2K or H-2D gene product and is responsible for the reversible variation in the reactivity of the tumor cells with T cells. (Author abstract) (22 Refs)

292. ELICITATION OF ANTI-SENDAI VIRUS CYTOTOXIC T LYMPHOCYTES BY VIRAL AND H-2 ANTIGENS INCORPORATED INTO THE SAME LIPID BILAYER BY MEMBRANE FUSION AND BY RECONSTITUTION INTO LIPOSOMES.

Hale AH, Lyles DS, Fan DP

Dept. Microbiology, Bowman Gray Sch. Medicine, Winston-Salem, NC, 27103

J Immunol; 124(2):724-731 1980

We have investigated the minimal molecular requirements for elicitation of anti-Sendai virus cytotoxic T lymphocytes (CTL), and the minimal molecular requirements for the recognition and lysis processes associated with anti-Sendai virus CTL-target cell interactions. This report demonstrates a) that the hemagglutinin-neuraminidase and/or fusion glycoproteins of Sendai virus can elicit anti-Sendai virus CTL and b) that these glycoproteins and H-2 antigens must be within the same membrane lipid bilayer for effective elicitation of anti-Sendai-virus CTL and for effective recognition and lysis of target cells by anti-Sendai virus CTL. (Author abstract) (26 Refs)

293. ELICITATION OF ANTI-VIRAL CYTOTOXIC T LYMPHOCYTES WITH A PURIFIED ANTIGEN (MEETING ABSTRACT).

Hale AH

Bowman Gray Sch. Medicine, Winston-Salem, NC, 27103

Fed Proc; 38(3,part2):1165 1979

Cytotoxic T lymphocytes (CTLs) specific for the expression of the major surface glycoprotein (G protein) of vesicular stomatitis virus (VSV), are elicited by iv injection of live VSV. In this report, we describe experiments where secondary CTLs, specific for VSV infected target cells, are elicited by in vitro stimulation with purified G protein. Spleen cells from VSV primed BALB/c, BALB.B, BALB.HTG and (BALB/c x BALB.B) F1 mice were incubated with solubilized (detergent) or *particulate (liposomal)* purified G protein. G protein was incorporated by dialysis (48 hr) into 3 different types of liposomes made of egg lecithin, cell membrane lipids or egg lecithin plus 10% cholesterol. Approx 50% of the G protein was exposed on the surface of the liposomes. G protein incorporated into liposomes from cell membrane lipids or egg lecithin plus cholesterol more effectively elicited an anti-VSV effector cell response than G protein incorporated into egg lecithin alone. The results indicate that these effectors are T cells and that appropriate target cells require the expression of the VSV G protein for lysis to occur. These CTLs are also H-2 restricted for their lytic function and recognize, in association with the viral specific antigens, both the H-2K and/or H-2D gene products. (no Refs)

294. MOLECULAR ASSOCIATION OF A VIRUS PROTEIN AND TRANSPLANTATION ANTIGENS ON TUMOUR CELL LINES (MEETING ABSTRACT).

Kvist S, Ostberg L, Curman B, Persson H, Philipson L, Peterson PA

Dept. Cell Res., Uppsala Univ., Uppsala, Sweden

Scand J Immunol; 8(2):162 1978

It is now well established that T-killer cells may be raised against virus-infected, syngeneic cells. This has led to the idea that the T-killer cells, which display H-2-restricted killing, either have one receptor recognizing 'altered self' structures or have two receptors, 'dual recognition', interacting independently with H-2 K/D antigens and virus antigens. To decide between these two possibilities, we have initiated studies on several adenovirus-transformed rat and hamster

cell lines. These cell lines express an 'early transcript' virus-coded protein (E19) which appears physically linked to the classical transplantation antigens. Thus, rabbit antisera or alloantisera against the classical transplantation antigens precipitate, as expected, the classical transplantation antigens, but in addition the E19 virus protein co-precipitated. Moreover, neither of the antisera reacts directly with the isolated E19 protein. Gel chromatography separations and reconstitution experiments with use of *artificial membranes and liposomes* corroborate the physical interaction between the classical transplantation antigens and the E19 protein. The tumor cell lines may be killed by T-killer cells raised in syngeneic recipients. These data argue for the T-killer cell recognizing foreign structures as 'altered self' by one receptor rather than by 'dual recognition'. (no Refs)

295. HUMAN (HLA-A AND HLA-B) AND MURINE (H-2K AND H-2D) HISTOCOMPATIBILITY ANTIGENS ARE CELL SURFACE RECEPTORS.

Helenius A, Morein B, Fries E, Simons K, Robinsons P, Schirrmacher V, Terhorst C, Strominger JL
European Molecular Biology Lab., Postfach 10 2209, D-6900 Heidelberg, W. Germany
Proc Natl Acad Sci USA; 75(8):3846-3850 1978

The proteins for the HLA-A and HLA-B loci in man and the H-2K and H-2D loci in mice were identified as cell surface receptors for Semliki Forest virus. This conclusion is based on the following observations: (i) Water-soluble octamers of viral coat proteins inhibit the complement-dependent cytotoxicity of antibodies directed against H-2K and H-2D antigens in mouse cells. (ii) Isolated detergent-soluble HLA-A and HLA-B antigens reconstituted in *lipid vesicles* inhibit the binding of viral protein to human cells (as do the water-soluble antigens to a lesser extent). (iii) Reconstituted HLA-A and HLA-B vesicles interact in solution with Semliki Forest virus (or with vesicles containing viral spike proteins), as demonstrated by coprecipitation with antisera. (iv) Complexes between viral spike proteins and HLA-A and HLA-B antigens or H-2K and H-2D antigens can be isolated from the cell surface by utilizing affinity chromatography or immunoprecipitation. (Author abstract) (36 Refs)

296. STUDIES ON LYMPHOCYTE-MEDIATED CYTOLYSIS. XII. HAPTEN TRANSFERRED TO CELL SURFACES BY INTERACTION WITH LIPOSOMES IS RECOGNIZED BY ANTIBODY BUT NOT BY HAPTEN-SPECIFIC H-2 RESTRICTED CYTOTOXIC T CELLS.

Ozato K, Henney CS
Dept. Medicine, Johns Hopkins Univ. Medical Sch., Baltimore, MD
J Immunol; 121(6):2405-2412 1978

Lymphocyte and mastocytoma (P815) cell populations incubated with dinitrophenyl (DNP)-phosphatidylethanolamine in the form of liposomes displayed cell surface hapten as evidenced by: i) 125I-anti-DNP antibody binding; ii) complement-mediated lysis, and iii) killer (K)-cell mediated lysis. Under optimal conditions, P815 cells incubated with DNP-liposomes showed a higher DNP density than was obtained by direct surface haptenation with dinitrobenzene sulfonic acid (DNBS). Moreover, the DNP transferred via cell-liposome interactions persisted on the cell surface at least as long as that introduced by DNBS. Despite ready accessibility to antibody, the cell surface hapten introduced by cell-liposome interaction was not recognized by hapten-specific cytotoxic T cells. Thus, cells bearing liposome-derived (DNP)- (or trinitrophenyl (TNP-) could not serve as targets for H-2 restricted hapten-specific effector cells; did not competitively inhibit the lysis of DNBS- (or trinitrobenzene sulfonic acid- (TNBS)) modified cells; and, furthermore, did not stimulate hapten-specific cytotoxic cells in either primary or secondary responses. Interestingly, membrane preparations obtained from TNBS-treated cells did not 'trigger' primary or secondary hapten-specific cytotoxic responses, although the same preparations readily stimulated 'primed' allogeneic cells. In contrast to the results obtained with cells bearing lipid-associated hapten, the addition of haptenated (DNP- or TNP-) bovine serum albumin (BSA) to lymphocyte cultures readily stimulated H-2 restricted, hapten-specific, cytotoxic T cell production. Cells incubated with DNP- (or TNP-) BSA for even brief (60 to 90 min) periods became susceptible to attack by syngeneic hapten-specific effector cells and specifically inhibited the lysis of syngeneic cells modified with the appropriate nitrobenzene sulfonic acid. These findings illustrate several features of target cell recognition by hapten-specific, H-2 restricted, cytotoxic T cells: i) hapten display on the cell surface is an insufficient requirement per se, even when present on a cell of appropriate H-2 genotype, and ii) hapten and H-2 do not have to be present on the same molecule on the target cell surface. These observations favor the proposition that hapten and H-2 associated antigens are recognized distinctly by the cytotoxic T cell. (Author abstract) (25 Refs)

297. MARKED STIMULATION OF LYMPHOCYTE-MEDIATED ATTACK ON TUMOR CELLS BY TARGET-DIRECTED LIPOSOMES CONTAINING IMMUNE RNA.

Magee WE, Cronenberger JH, Thor DE
Div. Allied Health and Life Sciences, Univ. Texas, San Antonio, TX, 78285
Cancer Res; 38(4):1173-1176 1978

Lymphocytes from normal Sewall-Wright strain 2 guinea pigs were tested for cytotoxicity against line 10 ascites hepatocarcinoma cells by a Cr release test. Lymphocyte-mediated cytotoxicity was greatly increased by preincubation with liposomes (containing sphingomyelin, cholesterol, dicetyl phosphate, and stearylamine; negative liposomes lacked stearylamine) containing both the anti-lymphocyte antibody (IgG) to provide 'homing' of the vesicles and immune RNA isolated from guinea pigs immunized with line 10 cells. These vesicles were much less cytotoxic to line 1 hepatoma cells. Liposomes directed against line 1 cells and containing actinomycin D (A-D: approx 50 ug/ml) were highly cytotoxic to line 1 cells. They showed somewhat more cross-reactivity (against line 10 cells) than in the case of anti-line 10 IgG-containing vesicles incubated with line 1 cells. Liposomes containing only entrapped antibody or A-D were not cytotoxic to either tumor type. This target cell delivery of immune RNA by liposomes caused a dose-dependent stimulation of lymphocyte-mediated cytotoxicity, up to 12x higher than that obtained by in vitro methods using naked immune RNA. (18 Refs)

298. LIPID MODEL MEMBRANE STUDIES ON IMMUNE CYTOTOXIC MECHANISM.

Blumenthal R, Weinstein JN, Henkart P
Lab. Theoretical Biology, NIH, NCI, Bethesda, MD 20014
Adv Exp Med Biol; 84:495-507 1977

A system based on the planar lipid bilayer in which mechanisms of lymphocyte-mediated cytotoxicity can be investigated is introduced. Planar bilayer lipid membranes (BLM) are advantageous in that electrical measurements are extremely sensitive and in that concentrations on both sides of the membrane, as well as the membrane potential, can easily be controlled. In bilayers containing a hapten, human lymphocytes induce an increase in membrane ion permeability if

specific antibody is added. This increase requires the membrane voltage to be positive on the lymphocyte side of the membrane; this is the case with target cell membranes. Conductance changes in the BLM follow the cellular and antibody requirements of the lymphocyte-mediated lysis of target cells: lymphocytes resting on the BLM in the absence of antibody did not induce significant conductance changes. The data indicated that killer lymphocytes act on membranes directly, causing permeability increases without the participation of the other target cell components. Membrane potential measurements in different salt concentrations suggested that the conductance-inducing material had a selectivity for anions over cations. (21 Refs)

299. DAMAGE OF LIPOSOMES IN ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

Juy D, Billecocq A, Faure M, Bona C
Inst. Pasteur, Experimental Immunotherapy, 28 rue du Dr. Roux, 75724 Paris, Cedex 15, France
Scand J Immunol; 6(6/7):607-614 1977

The antibody-dependent cytotoxicity of lymphocytes against liposomes composed of sphingomyelin, cardiolipin, and cholesterol was investigated. It was found that sphingomyelin, cholesterol, and cardiolipin liposomes coated with cardiolipidic antibodies could be destroyed by spleen or thymus cells. Lymphoid cells with Fc receptors are able to lyse antibody-coated target cells in an antibody-dependent cell-mediated cytotoxicity reaction. (29 Refs)

300. THE USE OF ANTIBODY-COATED LIPOSOMES AS A TARGET CELL MODEL FOR ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY.

Geiger B, Schreiber AD
Dept. Biology, Univ. California at San Diego, La Jolla, CA, 92093
Clin Exp Immunol; 35(3):149-154 1979

A simple model system was developed for antibody-dependent cell-mediated cytotoxicity (ADCC) using antibody-coated synthetic membranes (liposomes) as a target cell model. A synthetic hapten, dinitrophenyl-phosphatidylethanolamine (DNP-PE), was incorporated into fluorophore-quencher-loaded liposomes and the latter were coated with pure anti-DNP antibodies. Normal, spleen lymphocytes were capable of binding and subsequently lysing these liposomes. This process is dependent upon the presence of an intact [crystallizable fragment (Fc)-containing] IgG molecule and independent of exogenous serum complement. The effector lymphocytes are nylon nonadherent, devoid of Thy-1 antigen and present in nude mice, suggesting an identity with K (Fc receptor positive) lymphocytes. These studies indicate that liposomes may be used as a model to study the requirements for the binding and lysis of target cells in this cell-mediated cytotoxic system. (Author abstract) (27 Refs)

301. INTEGRATION OF A VIRUS MEMBRANE PROTEIN INTO THE DOUBLE LIPID LAYER OF THE TARGET CELLS APPEARS TO BE ESSENTIAL FOR ANTI-VIRAL IMMUNE CYTOLYSIS (MEETING ABSTRACT).

Morein B, Barz D, Schirrmacher V
Natl. Veterinary Inst., Stockholm, Sweden
Scand J Immunol; 10(4):374-375 1979

The requirements of viral antigen expression on target cells in antibody-dependent cell lysis in the presence of complement (CDL) or K cells (ADCC) were studied. We have used the membrane protein of Semliki Forest virus (SFV) and the tumor cells P815 and Eb in our model system. The SFV membrane protein can be prepared as practically detergent- and lipid-free protein micelles in octamer forms or reconstituted into lipid vesicles sc virosomes. Three types of target cells were prepared: virus membrane protein attached to receptors on the cell surface as protein micelles or as virosomes under nonfusion conditions; virus protein integrated in the cell membrane from inside by infection; and virus protein integrated in the cell membrane from outside by fusion of virosomes with aid of Sendai virus as fusion factor. The lysis of the cells in the CDL and ADCC assays was measured with the 51CR release technique. Cells expressing the virus antigen attached to virus receptors on the cells were not lysed by antivirus antibodies in the immune lysis tests, while cells bearing the viral membrane protein integrated in the lipid layers of the cell membrane by fusion from outside or by infection were lysed in the CDL and ADCC assays. (no Refs)

302. CELLULAR RECOGNITION AND TRIGGERING BY MOBILE HAPTENS IN MODEL MEMBRANES (MEETING ABSTRACT).

McConnell HM, Parce JW, Hafeman D, Lewis JT, Humphries GM
Dept. Chemistry, Stanford Univ., Stanford, CA, 94305
Biophys J; 25(2,part2):1a 1978

It has been known for a long time that a multiplicity of haptens, bound to a relatively rigid carrier such as a protein, can elicit a variety of immunoglobulin-dependent immune responses, whereas free haptens in soln do not. This has led to the view that multivalent hapten-mediated intermolecular cross-linked immunoglobulins provide unique efferent and afferent signals for the immune system. Our studies of complement and cellular immune responses to lipid bilayer membranes containing laterally mobile haptens provide another view of the critical molecular events involved in antibody-dependent immune responses. Thus, we have found that laterally mobile nitroxide spin-label lipid haptens in *lipid vesicles and liposomes* can trigger specific in vitro antibody-dependent immune responses of complement, neutrophils, and macrophages. (Dinitrophenyl-lipid haptens in liposomes can also stimulate a primary in vitro B cell response). In these lipid systems the antibodies bound to mobile lipid haptens are randomly distributed on the vesicle membrane surface, and have effectively only intramolecular cross links. The antibodies are evidently activated by a conformational change upon binding to membrane bound lipid haptens and then bind to and presumably activate Fc receptors on the neutrophils and macrophages. The trigger signal for cellular response may require subsequent lateral associations of activated Fc receptors as might be inferred from cellular triggering by insulin and Fc receptors in adipocytes and mast cells. (no Refs)

303. SPECIFICITY OF MEMORY CELLS RAISED AGAINST TRINITROPHENYL-CONJUGATED SYNGENEIC CELLS.

Maeda T, McConnell HM
Dept. Biochemistry, Div. Biological Sciences, State Univ. New York at Stony Brook, Stony Brook, NY, 11794
Proc Natl Acad Sci USA; 76(4):1537-1541 1979

Exogenous lipid analogues can be incorporated into purified plasma membranes of EL4 tumor cells. When EL4 membranes are incubated with *sonicated lipid vesicles* containing spin-labeled phosphatidylcholine and then purified, they exhibit paramagnetic resonance spectra characteristic of spin labels dilutely dispersed in the lipid bilayer. Also, when EL4 membranes are incubated with vesicles of fluorescent lipid (N-4-nitrobenzo-2-oxa-1,3-diazole phosphatidylethanolamine), the fluorescence intensity of the

mixture gradually increases and the labeled membranes are strongly fluorescent under a microscope, whereas the original lipid vesicles are much less fluorescent because of self-quenching at the high relative concentration of the fluorophore in the vesicles (33%, wt/wt). Thus, lipid analogues can be integrated into the bilayers of EL4 plasma membranes. The ability of the EL4 membranes containing trinitrophenyl phosphatidylethanolamine to induce a secondary proliferation of C57BL/6 mouse spleen lymphocytes primarily stimulated by trinitrophenyl-modified autologous cells was investigated. Although trinitrophenyl-modified plasma membranes as well as trinitrophenyl-modified lymphocytes or EL4 cells caused a specific, H-2 restricted response, membranes containing trinitrophenyl phosphatidylethanolamine did not induce a secondary proliferative response. Because of the strong likelihood that all three lipid analogues mentioned above are similar to one another in having a high lateral mobility and in not being strongly associated with H-2 cell-surface molecules, these results can be viewed, with caution, as being consistent with a 'modified self' model rather than a dual recognition model for H-2 restriction in the cell-mediated immune response to chemically modified syngeneic cells. (Author abstract) (49 Refs)

304. MODULATION OF THE IMMUNE RESPONSE BY ANTIGEN-REACTIVE LYMPHOCYTES AFTER CULTIVATION WITH GANGLIOSIDES.

Miller HC, Esselman WJ

Dept. Microbiology, Michigan State Univ., East Lansing, MI 48824

J Immunol; 115(3):839-843 1975

GM1 ganglioside isolated from mouse brain was capable of inhibiting the thymocytotoxicity of AKR anti-Thy 1.2 antiserum and to a lesser extent anti-BAtheta antiserum. GD1 b ganglioside of mouse brain and thymocytes inhibited the thymocytotoxicity of rabbit anti-BAtheta antiserum for mouse thymocytes. When GM1 ganglioside, in the form of cholesterol-lecithin *liposomes*, was incubated with spleen cell cultures in the presence of SRBC, depressed anti-SRBC hemolytic plaque responses were observed. This effect could be neutralized by first absorbing the GM1 liposomes with anti-Thy-1.2 antibodies. The kinetics of GM1 suppression of spleen cell cultures reveal reduced plaque-forming cell numbers when the ganglioside was added even as late as the 4th day of culture. Results of experiments in which GM1 ganglioside was incubated with either bone marrow cells or with thymocytes suggest that the target cell for GM1 liposomes is the B lymphocyte.

305. ON THE IMMUNE PRECIPITATION OF PHOSPHORYLCHOLINE LIPIDS WITH TEPC 15 MOUSE MYELOMA PROTEIN AND WITH ANTI-LECITHIN SERA FROM GUINEA PIGS.

Niedieck B, Kuck U, Gardemin H

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Immunochemistry; 15(7):471-475 1978

The BALB/c mouse myeloma protein TEPC 15 (T 15) and sera of guinea pigs immunized with lecithin (lec) precipitate in agarose gels with mixed micelles bearing the phosphorylcholine lipids (PC-lipids) lec, lysolecithin and sphingomyelin. The T 15 IgA and the guinea pig anti-lec antibody are both totally inhibited in agarose gels containing phosphorylcholine. The advantages of defined PC-lipids in contrast to the commonly employed complex antigens for the detection of anti-PC immunoglobulins are discussed. (Author abstract) (28 Refs)

306. CHARACTERIZATION OF ANTI-FORSSMAN (ANTI-FS) ANTIBODIES IN HUMAN SERA: THEIR SPECIFICITY AND POSSIBLE CHANGES IN PATIENTS WITH CANCER.

Young WW, Hakomori SI, Levine P

Dept. Pathobiology, Univ. Washington, Seattle, Washington

J Immunol; 123(1):92-96 1979

The majority of normal human sera hemolyze sheep RBC's in the presence of complement ('hemolyzers'), whereas sera of the remaining population do not lyse sheep RBC's ('nonhemolyzers'). The antibodies responsible for this lytic activity are now identified as being specific to Forssman (Fs) glycolipid, predominantly of the IgM class, and only weakly cross-reactive with blood group A glycolipid. These conclusions are based on the following observations: 1) 'Hemolyzer' sera produced complement-dependent *lysis of liposomes* containing Fs glycolipid, whereas 'nonhemolyzer' sera reacted very weakly with the same Fs liposomes; the level of hemolytic activity generally paralleled the reactivity of the sera with Fs liposomes. 2) Human 'anti-Fs' did not cross-react with liposomes containing either globoside, the precursor to Fs, or blood group A glycolipid. 3) The complement-dependent hemolysis of sheep RBC's by hemolyzer sera was specifically inhibited by Fs liposomes but not by either A- or globoside liposomes. 4) In five of six cases tested, hemolysin activity was present in the IgM fraction but not the IgG fraction, whereas in the remaining case the activity was present in the IgG fraction. We have previously described the presence of Fs glycolipid in the normal gastrointestinal mucosa of a minor percentage of Taiwanese cancer patients, whereas in the majority of cases Fs was absent in the normal mucosa but present in the tumors derived therefrom. The sera of cancer patients displayed a decreased anti-Fs reactivity as compared with sera of a control group suggesting that Fs-positive tumor tissue may affect serum anti-Fs levels. (Author abstract) (27 Refs)

307. ISOANTIGENIC EXPRESSION OF FORSSMAN GLYCOLIPID IN HUMAN GASTRIC AND COLONIC MUCOSA: ITS POSSIBLE IDENTITY WITH 'A-LIKE ANTIGEN' IN HUMAN CANCER.

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Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104

Proc Natl Acad Sci USA; 74(7):3023-3027 1977

The Forssman glycolipid and its precursor globoside were examined in 21 samples of surgically removed gastrointestinal mucosa and tumors. Hemolysis inhibition and *liposome lysis assays* of the ceramide tetrasaccharide and pentasaccharide fractions of the 21 samples indicated that 16 patients lacked Forssman activity (F-) and 5 showed positive activity (F+). The F- population included blood groups A, B, and O, but none of the F+ group belonged to blood group A. All tumors derived from F- mucosa contained significant levels of Forssman reactivity, but none of the tumors originating in F+ mucosa contained Forssman glycolipid. Globoside, the immediate precursor of Forssman antigen, was distributed equally among F+ and F- mucosa and tumors. The expression of the Forssman antigen in gastrointestinal mucosa appears, therefore, similar to that of an isoantigen and could represent a human tumor-associated antigen. In view of the well-known strong cross reactivity of Forssman antigen with blood group A determinants, it is suggested that the appearance of Forssman antigen in human tumors could be related to the previously described 'A-like antigen' (or neo-A antigen) of human tumors. (32 Refs)

308. ACTIVATION OF HUMAN COMPLEMENT BY LIPOSOMES: SERUM FACTOR REQUIREMENT FOR ALTERNATIVE PATHWAY ACTIVATION.

Mold C, Gewurz H
Dept. Immunology, Rush Univ., Chicago, IL, 60612
J Immunol; 125(2):696-700 1980

Liposomes were shown previously to activate human C by the alternative pathway. The most active liposomes contained dimyristoyl phosphatidylcholine (DMPC), cholesterol (CHOL), stearylamine (SA), and galactosyl ceramide. C3 conversion produced in C2-deficient serum by incubation with liposomes was affected by changes in CHOL concentration and phospholipid fatty acyl composition and required SA and a glycolipid. Antibody was not required for activation, since C3 conversion by liposomes was observed in serum lacking immunoglobulin. However, preadsorption of serum with liposomes abolished the capacity of liposomes to activate the alternative pathway without affecting activation by LPS or rabbit RBC. Although a liposome-adsorbable serum factor was required for C3 conversion by liposomes, it was not sufficient for activation. Liposomes lacking glycolipid or CHOL could adsorb the serum factor but did not activate the alternative pathway. The serum factor could also be adsorbed by phosphocholine-Sepharose beads. These experiments suggested that the binding site for the serum factor on the liposomes was the phospholipid, DMPC. Studies testing the inhibition of serum factor binding by substances with structural similarity to phosphatidylcholine supported this hypothesis: binding was inhibited by phosphocholine and glycerophosphocholine. Although the role of the serum factor in activation is not known, liposomes containing dimyristoyl phosphatidylethanolamine in place of DMPC no longer require adsorbable serum factors to activate the alternative pathway. These findings indicate an important role for the membrane phospholipid in the activation of the alternative pathway by liposomes. (Author abstract) (23 Refs)

309. BINDING OF HLA ANTIGEN-CONTAINING LIPOSOMES TO BACTERIA.

Klareskog L, Banck G, Forsgren A, Peterson PA
Dept. Cell Res., Univ. Uppsala, Box 575, S-751 23 Uppsala, Sweden
Proc Natl Acad Sci USA; 75(12):6197-6201 1978

Highly purified, detergent-solubilized human leukocyte antigen (HLA)-A and -B antigens and HLA-D antigens were separately incorporated into liposomes. Detergent-solubilized transplantation antigens, but not papain-solubilized antigens lacking the membrane-integrated portions of the molecules, were bound to the liposomes. A considerable portion of the liposome-bound antigens displayed accessible antigenic sites, suggesting that they were oriented in the right-side-out direction. Liposomes containing the HLA-A and -B antigens or the HLA-D antigen interacted similarly with bacteria. The two types of liposomes bound efficiently to two strains of Neisseria catarrhalis (now classified as Branhamella catarrhalis) and to one strain of Haemophilus infuenzae, weakly to one strain of Escherichia coli, and not at all to another strain of E coli. The binding between the HLA antigen-containing liposomes and one strain of N catarrhalis was abolished when Fab fragments directed against the heavy chains of HLA-A and -B antigens or against HLA-D antigens, respectively, were added. In contrast Fab fragments against beta2-microglobulin did not measurably impede the bacteria-liposome interaction, suggesting that, with regard to the HLA-A and -B antigens, the heavy, but not the light chains interacted with the bacteria. Additional experiments showed that N catarrhalis preferentially interacted with transplantation antigens when mixed with detergent-solubilized lymphocyte membrane glycoproteins. These data suggest that HLA-A and -B and HLA-D antigens may have the function of interacting with foreign antigens such as bacteria. (Author abstract) (23 Refs)

IX. USE OF LIPOSOMES TO STUDY CELL MEMBRANE PROPERTIES

A.

Liposomes in investigations of membrane viscosity and fluidity

310. THE REGULATION OF MEMBRANE LIPID FLUIDITY BY MEMBRANE LIPID BIOSYNTHESIS.

Sinensky MS
Eleanor Roosevelt Inst. Cancer Res., Denver, CO
Adv Pathobiol; 7:365-376 1980

Several important compositional determinants of phospholipid acyl chain mobility have been discovered using order parameter measurement techniques in *model lipid mixes*. The acyl chains become less mobile as fatty acyl substituents become longer and more saturated. Above the solid to liquid crystalline transition, increasing cholesterol decreases acyl chain mobility. Below this transition, it increases acyl chain mobility. In many poikilothermic organisms, there is an increase in the proportion of saturated and longer-chain fatty acids in membrane phospholipids with increasing temperature of growth. Acyl chain mobility increases exponentially with temperature, and the variation of fatty acid of membrane phospholipids may produce membranes with constant fluidity at the temperature of growth, called 'homeoviscous adaptation'. In Escherichia coli, this variation in fatty acid composition results in a constant lipid acyl chain mobility at the temperature of growth. It is hypothesized that a Chinese hamster ovary cell mutant (CHO-CR1) which is resistant to the killing effects of 25-hydroxycholesterol is defective in the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase synthesis by cholesterol derivatives. The defect in the ability to regulate cholesterol synthesis has led to a corresponding defect in an ability to regulate plasma membrane fluidity. It was found that the observed rate constant for an enzymatic reaction was inversely related to the rotational correlation time of an enzyme embedded within the lipid bilayer. The effect of cholesterol on the CR1 mutant is mediated through fluidity changes and is not due to a direct chemical effect of cholesterol on the enzyme. (24 Refs)

311. DOES FLUORESCENCE POLARIZATION REVEAL FLUIDITY OR MEMBRANE PROTEIN CHANGES? (MEETING ABSTRACT).

Mely-Goubert B, Calvo F, Rosenfeld C
Institut de Cancerologie, Villejuif, France
Abstracts of the 5th Meeting of the European Association for Cancer Research, held in Vienna, Austria, September 9-12, 1979. European Association for Cancer Research, Vienna, Austria, 83 pp., 1979.

Membrane fluidity is associated to steady state fluorescence polarization (FP) of a widely used, completely apolar (but highly polarizable) fluorescent probe: 1,6-diphenyl-1,3,5-hexatriene (DPH). We analyze the relevance of such a correla-

tion on the grounds of FP experiments with systems of growing complexity; soap bilayers, *phospholipid liposomes* and whole cells, and on theoretical evidences on intermolecular energies involved. We conclude that it is not the fluidity of the membrane which is reflected in FP values but rather specific interactions of DPH molecules in the hydrophobic part of the bilayers. Our data on denaturation experiments of DPH-labeled bovine serum albumin support the assumption that hydrophobic regions of proteins are involved. Differences reported by several authors between FP values of normal and leukemic cells could thus reveal differences in 'hydrophobic pockets' of membrane proteins. (no Refs)

312. ROTATIONAL RELAXATION OF 1,6-DIPHENYL-HEXATRIENE IN MEMBRANE LIPIDS OF CELLS ACCLIMATED TO HIGH AND LOW GROWTH TEMPERATURES.

Martin CE, Foyt DC
Dept. of Botany, Univ. of Texas, Austin, Texas, 78712
Biochemistry (Washington); 17(17):3587-3591 1978

Measurement of the time-resolved fluorescence depolarization of 1,6-diphenylhexatriene (DPH) in *artificial bilayers* of microsomal membrane lipids from Tetrahymena gives detailed information concerning the molecular motion of this probe and fluid properties of the membrane lipids which are obscured with steady-state methods. The rotational motion of DPH in these lipids from cells acclimated to 15 and 39.5 C growth temperatures was anisotropic, which agrees with recent time-resolved studies of this probe in synthetic phospholipid systems. Evaluation of DPH polarization data obtained from these lipid fractions at their respective growth temperatures showed differences in physical properties which suggest that 'viscosity', per se, of the microsomal lipids is not as strictly regulated as it is in prokaryotic systems. Rotational relaxation of DPH in 39.5 C microsomal lipids measured at 15 C is more complex than that of either lipid fraction measured at its actual growth temperature, suggesting that the probe has partitioned into two dissimilar environments within the bilayer. Similar effects are observed in the microsomes of 39.5 C cells by freeze-fracture electron microscopy following rapid cooling to 15 C. Under these conditions, two distinct regions are observed on the fracture faces, suggesting a correlation between lipid phase changes and alterations in membrane structure. (Author abstract) (14 Refs)

313. DECREASED MICROVISCOSITY OF MEMBRANE LIPIDS IN LEUKEMIC CELLS: TWO POSSIBLE MECHANISMS.

Petitou M, Tuy F, Rosenfeld C, Mishall Z, Paintrand M, Jasnin C, Mathe G, Inbar M
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Proc Natl Acad Sci USA; 75(5):2306-2310 1978

Steady-state fluorescence polarization studies with the fluorescent lipid probe 1,6-diphenyl 1,3,5-hexatriene were done to determine the degree of microviscosity of cellular membrane lipids and serum lipoproteins in human normal donors and leukemic patients. The results show a marked decrease in microviscosity of cellular membrane lipids in both intact lymphocytes and isolated cellular plasma membranes obtained from leukemic patients in clinical relapse as compared to intact lymphocyte and isolated cellular plasma membranes obtained from normal donors and leukemic patients in complete clinical remission. Concomitant to these dynamic changes in cellular membrane lipids, the degree of microviscosity of lipids in the blood serum of leukemic patients in clinical relapse is markedly reduced as compared to serum obtained from normal donors and leukemic patients in complete clinical remission. Moreover, an in vitro incubation of leukemic lymphocytes with normal low density lipoproteins results in an increased microviscosity of cellular membrane lipids. In addition to the interrelation between cellular membrane lipids and serum lipoproteins, plasma membrane vesicles with a high degree of lipid microviscosity were isolated from the blood serum and pleural effusion of leukemic patients in clinical relapse. Such membrane vesicles could not be detected in normal serum. Therefore, we suggest that the two major mechanisms associated with the decreased microviscosity of membrane lipids in human leukemic cells are an abnormal exchange in lipids between the leukemic cell surface membrane and leukemic serum lipoproteins and an exfoliation of plasma membrane vesicles with a high degree of microviscosity from the cell surface of leukemic cells. (Author abstract) (35 Refs)

314. FLUIDITY OF MEMBRANE LIPIDS IN HUMAN LYMPHOBLASTOID CELL LINES (MEETING ABSTRACT).

Petitou M, Tuy F, Rosenfeld C, Inbar M
Departement de Cancerologie et d'Immunogenetique, Villejuif, France
Fourth Meeting of the European Association for Cancer Research Held at Universite de Lyon, September 13-15, 1977. European Association for Cancer Research, Lyon, France 1977.

Plasma membranes were isolated from two human lymphoblastoid cell lines, LHN13 and REH, established from normal and leukemic lines respectively. The isolated membranes as well as *liposomes* prepared from their lipid extracts were subjected to fluorescence polarization analysis using the fluorescent hydrocarbon probe 1.6 diphenyl 1,3,5-hexatriene (DPH). From the recorded degree of fluorescence polarization (P) of the DPH-labeled membranes or liposomes the degree of membrane lipid microviscosity (M) was determined. The results show a marked decrease in both P or M values in membranes or liposomes obtained from the REH cells as compared to membranes of liposomes obtained from the LHN13 cells. These results are in accord with the notion that leukemic transformation of lymphoid cells is accompanied by an increase in the degree of fluidity of the plasma membrane lipid core. (no Refs)

315. DECREASED MEMBRANE FLUIDITY AS A FACTOR IN LYMPHOCYTE RESPONSE IN AGING (MEETING ABSTRACT).

Rivnay B, Friedman D, Shinitzky M, Globerson A
Weizmann Inst. Science, Rehovot, Israel
Isr J Med Sci; 13(10):1060 1977

It has recently been demonstrated that mitogenic response of spleen lymphocytes is affected by elevation of cholesterol levels in the plasma membranes. Since immune responses decrease in aging and since there have been reports on elevated serum cholesterol concentration in the old, a possible correlation between the two phenomena was tested. Cholesterol is exchangeable between serum components and RBC plasma membranes. Accordingly, it was assumed that such a process takes place in aging lymphocytes as well, leading to changes in the membrane cholesterol and viscosity, and to lowered capacity of these cells to respond to mitogenic stimulation. The elevated viscosity of spleen cells of old mice compared with young was verified. It was also shown that by treatment with *lecithin-liposomes* to lower relative cholesterol concentration in the plasma membrane some improvement in the response to mitogens could be obtained. Lipid analysis is currently being performed on both sera and

plasma membranes. These observations indicate that lipid blood components may affect immune reactivity of lymphocytes.

316. FLUIDITY OF MEMBRANE LIPIDS: A SINGLE CELL ANALYSIS OF MOUSE NORMAL LYMPHOCYTES AND MALIGNANT LYMPHOMA CELLS.

Inbar M
Dept. Membrane Res., Weizmann Inst. Science, Rehovot, Israel
FEBS Lett; 67(2):180-185 1976

To determine membrane fluidity in normal and malignant cells on a single cell level, a method was used that is based on the fluorescence polarization of a fluorescent probe, 1,6-diphenyl 1,3,5-hexatriene (DPH). Since the fluorescence signals of DPH labeled cells are predominantly obtained from DPH molecules located only in the cell surface membrane lipid core, this method can be used in the dynamic study of cell surface membrane changes. Normal lymphocytes were obtained from spleen or thymus of A strain mice; lymphoma cells were from an ascites form of Moloney-virus-induced lymphoma (YAC) grown in A mice. Fresh *liposomes* of lecithin or lecithin-cholesterol (1:1,m/m) were prepared for each experiment. One volume of freshly isolated cell suspension at a concentration of 10(7) cells/ml is mixed with one volume of 2 X 10(-6) M DPH dispersion, incubated at 37 C for 30 min, washed in phosphate-buffered saline (PBS) at pH 7.2, and resuspended in PBS to a concentration of 10(6) cells/ml. For labeling liposomes, one volume of liposomes is mixed with one volume of DPH dispersion prepared in 0.15 M KCl and incubated at 37 C for 30 min. Fluidity measurements of labeled cells were carried out at 25 C. In experiments carried out with normal and leukemic lymphocyte populations, malignant cells showed decreased fluorescence or a marked increase in fluidity caused by a decrease of the ratio of cholesterol to phospholipids in the cell surface membrane. In human leukemia, this can be correlated with the acuteness of the disease. When malignant lymphoma cells were treated with lecithin-cholesterol liposomes, fluorescence polarization increased or there was a decrease in membrane fluidity; biologically, this would result in a marked inhibition of their tumorigenicity. (22 refs)

317. DIFFERENCE IN MICROVISCOSITY INDUCED BY DIFFERENT CHOLESTEROL LEVELS IN THE SURFACE MEMBRANE LIPID LAYER OF NORMAL LYMPHOCYTES AND MALIGNANT LYMPHOMA CELLS.

Shinitzky M, Inbar M
Lab. Membr. Bioregul., Weizmann Inst. Sci., Rehovot, Israel
J Mol Biol; 85(1):603-615 1974

Microviscosity in the surface membrane lipid layer of normal rat and mouse lymphocytes and malignant murine lymphoma cells, and in *liposomes* prepared from their lipid extracts, was determined using the fluorescence polarization properties of 1,6-diphenyl-1,3,5-hexatriene embedded in the membrane lipid layer. The microviscosity values in both the intact cells and in the liposomes were distinctly greater for the normal lymphocytes than for the lymphoma cells, whereas the fusion activation energy in both cell types and their liposomes was 8 kcal/molecule. The relative cholesterol concentration in the lymphoma cells was about half that in the normal lymphocytes, a difference which might account for the difference in fluidity. This conclusion is supported by the observed changes in microviscosity, which followed artificial changes in the cholesterol concentrations in the surface membranes of both cell types. Introduction of exogenous cholesterol into the cell surface membranes was performed with lecithin-cholesterol (1:1) liposomes, and in the lymphoma cells resulted in an increase in microviscosity to the level of normal lymphocytes. Extraction of native cholesterol from the cell surface membranes via lecithin liposomes resulted in a decrease in microviscosity to the level seen in the lymphoma cells. By virtue of its control over the microviscosity of the lipid layers, the level of cholesterol in cell surface membranes may play an important role in determining the biological activities of normal and malignant cells.

318. INCREASE OF CHOLESTEROL LEVEL IN THE SURFACE MEMBRANE OF LYMPHOMA CELLS AND ITS INHIBITORY EFFECT ON ASCITES TUMOR DEVELOPMENT (MEETING ABSTRACT).

Inbar M, Shinitzky M
Lab. Membrane and Bioregul., Weizmann Inst., Sci., Rehovot, Isr
Proc Natl Acad Sci USA; 71(5):2128-2130 1974

An ascites form of malignant transformed lymphoma cells were treated in vitro with *liposomes* of 1:1 lecithin:cholesterol in order to increase the cholesterol level of the cell membranes, thereby increasing the rigidity of the lipid layer. This treatment inhibited the rate of killing by ascites tumor after ip inoc into adult A-strain mice of 10(4) and 10(5) treated cells/animal. With 10(3) treated cells/animal full survival was observed up to 90 d after inoc, whereas with the same number of untreated cells all mice were dead within 30 d. Analogous treatment with liposomes of pure lecithin did not inhibit the development of ascites growth from inoc of 10(3)-10(5) cells. Possible mechanisms of the effects of cholesterol on the tumor cell surface are discussed. (13 refs)

319. SIGNIFICANCE AND PROPERTIES OF SURFACE-DERIVED EXTRACELLULAR MEMBRANE VESICLES OF MURINE LEUKEMIA CELLS GROWN IN VIVO AND IN VITRO (MEETING ABSTRACT).

Van Blitterswijk WJ, Hilkmann H, Hilgers J, Feltkamp CA, Emmelot P
Div. Cell Biology, Netherlands Cancer Inst., Amsterdam, Netherlands
Program and Abstracts of the 12th International Leukocyte Culture Conference held in Beer Sheba, 25-30 June, 1978. Ben Gurion University of the Negev, Beer Sheba, Israel, 347 pp., 1978.

Extracellular vesicles, isolated from the ascites fluid of GR mice bearing 'GRSL' leukemia and from GRSL culture fluid, possess a much higher lipid rigidity than the plasma membranes isolated from the corresponding cells, due to a relatively high cholesterol and sphingomyelin content. The in vivo vesicles show enhanced expression of the mammary tumor virus-induced cell surface antigen, MLr. This antigen generates a host immune response against the tumor cells, that may thus be counteracted by these vesicles. A shift from low plasma membrane lipid fluidity in primary leukemias to high fluidity in later in vivo transplant generations has repeatedly been found. This shift may be the result of (immuno)selection mechanisms which eventually produce the rigid vesicles by shedding of selected cell surface domains and/or preferential killing of the most rigid cells in the population. In vitro cultures of GRSL cells also contain (even more) vesicles which are however generally much larger in size and enclose more intracellular elements, indicating that they are at least partly generated and/or processed in a different way. [3H]Fucose labeling experiments suggest that part(s) of these vesicles are endocytosed by the cells and by some recycling process are reinserted in the plasma membrane. (2 Refs)

320. DIFFERENCES IN LIPID FLUIDITY AMONG ISOLATED PLASMA MEMBRANES OF NORMAL AND LEUKEMIC LYMPHOCYTES AND MEMBRANES EXFOLIATED FROM THEIR CELL SURFACE.

Van Blitterswijk WJ, Emmelot P, Hilkmann HA, Oomenmeulemans EP, Inbar M
Netherlands Cancer Inst., Div. Cell Biology, Amsterdam, Netherlands

Biochim Biophys Acta; 467(3):309-320 1977

The lipid microviscosity of isolated plasma membranes of mouse thymus-derived ascitic leukemia (GRSL) cells and of the extracellular membranous vesicles exfoliated from these cells was determined to find out whether vesicle formation occurs from selected surface-membrane domains. The lipid microviscosity was also determined in isolated plasma membranes of normal thymocytes and extracellular membranes of thymus cell supernatants. The microviscosities were higher in the isolated plasma membranes of thymocytes and GRSL cells than in the corresponding intact cells. Microviscosities in the extracellular membranes of thymocytes and GRSL cells were even higher. The fluidity difference between these membranes and the plasma membranes was most pronounced for the leukemic cells and was correlated with a large difference in cholesterol/phospholipid molar ratio. There was little or no difference between the lipid fluidity in intact membranes of a given type and that in *liposomes* made from their lipid extracts, which may indicate that the presence of glycoproteins in the membrane has no effect on the dynamics of the lipid core. It is suggested that extracellular membranous vesicles are shed from the surface of GSRL cells similar to the budding process of viruses, by selection of the most rigid parts of the host cell membrane. (34 Refs)

321. MICROVISCOSITY CHANGES DURING DIFFERENTIATION OF NEUROBLASTOMA CELLS.

De Laat SW, Van Der Saag PT, Nelemans SA, Shinitzky M
Hubrecht Lab., International Embryological Inst., Utrecht, Netherlands

Biochim Biophys Acta; 509(1):188-193 1978

Microviscosity (n) of the plasma-membrane lipid matrix was measured in exponentially growing and differentiating C1300 mouse neuroblastoma cells, attached to a glass substratum, by fluorescence polarization of 1,6-diphenyl-1,3,5-hexatriene. Upon differentiation n decreases progressively, reaching values below those observed in the growth phase. Treatment of the cells with *dipalmitoyl phosphatidylcholine vesicles* reversibly inhibits morphological differentiation. The results show that a high membrane fluidity is a prerequisite for differentiation. (Author abstract) (8 Refs)

322. LEUKEMIC L-1210 CELL MEMBRANE MODIFICATIONS BY CHOLESTEROL TREATMENT.

Sentjurc M, Schara M, Nemec M, Cotic V, Pecar S, Sava G, Giraldi T
J. Stefan Inst., Univ. Ljublijana, Ljublijana, Yugoslavia

Stud Biophys; 75(1):13-24 1979

Mouse leukemic L-1210 cells were incubated with liposomes containing either lecithin (L) or L + cholesterol (C), and then labeled with one of two spin labels. Control L-1210 cells were not incubated with liposomes. Four normal mice received ip injections of 10(6), 10(5), 10(4), or 10(3) cells. Life spans of mice inoculated with tumor cells that had been incubated with either L or L + C liposomes increased relative to life spans of mice inoculated with unincubated L-1210 cells. Survival time increase over control dropped with lowered number of tumor cells in inoculum. Electron paramagnetic resonance (EPR) spectra for spin-labeled molecules incorporated into membranes of L-1210 cells showed only a small decrease in the plasma membrane fluidity of cells incubated with L + C liposomes, though the cholesterol content in those cells increased by 150% after incubation. L and C content of the liposomes and cells is given. The overall results showed that lengthening of animal survival time and decrease in cell membrane fluidity were due to liposome incubation, regardless of whether the liposomes were rich in L or L + C and that C made no significant difference in the results. (19 Refs)

323. MEMBRANE MICROVISCOSITY DIFFERENCES IN NORMAL AND LEUKAEMIC HUMAN LYMPHOCYTES.

Johnson SM, Kramers M
Div. Immunological Medicine, Clinical Res. Centre, Watford Road, Harrow, England

Biochem Biophys Res Commun; 80(2):451-457 1978

The membrane microviscosity of normal human tonsil lymphocytes, circulating blood mononuclear cells, and human chronic lymphocytic and acute lymphoblastic leukemia cells was studied using the fluorescent probe 1,6-diphenyl-1,3,5-hexatriene (DPH). The normal tonsil and acute lymphoblastic leukemia cells did not differ significantly with respect to DPH polarization. However, both were just significantly less than chronic lymphocytic leukemia cells, which were just significantly less than the circulating mononuclear cells; these findings cannot be correlated with leukemic transformation. The plasma membranes were more viscous than whole cells, and *liposomes* were only 57% as viscous as the plasma membranes from which they were prepared. The polarization degree of DPH in the lymphocytes was much lower and more variable than that of DPH in the platelets, polymorphonuclear WBC, and RBC membranes. (15 Refs)

324. IN VITRO AND PRELIMINARY IN VIVO STUDIES OF COMPOUNDS WHICH INDUCE THE DIFFERENTIATION OF FRIEND LEUKEMIA CELLS.

Preisler HD
Roswell Park Memorial Inst., Dept. Medicine A, Buffalo, NY 14263

Haematol Bluttransfus; 19:161-167 1976

In vitro and in vivo studies of chemical agents that induce the differentiation of Friend leukemia cells (FLC) are reported. The cryoprotective agents tetramethylurea, dimethylacetamide, N-methylacetamide, pyridine N oxide, dimethyl sulfoxide, dimethyl formamide, acetamide, dimethylurea, pyridazine, and diethylene glycol showed differentiation-inducing potencies (% of benzidine positive cells after 5 days of culture in the presence of the inducing agent) in FLC (line 745A) cultures ranging from 7% to 70%. All of these agents are small, polar, freely diffusible compounds. Although the compounds varied widely in their inducing potency, the biology of the differentiation process, once begun, appeared to be the same regardless of the inducing agent used. The differentiation of FLC in vitro was accompanied by the accumulation of globin messenger RNA, and it appears that any stimulus that induces FLC differentiation ultimately acts through the process of transcription. The ability of inducers to cryoprotect RBC suggests that these compounds also have significant effects on the cell membrane. Using differential scanning calorimetry, inducing cryoprotective agents were found to increase the melting temperature of artificial acidic *phospholipid vesicles*, indicating a decrease in the fluidity of the vesicle membranes. It appears that the initial event during the induction of differentiation by cryoprotective agents may occur at the cell

surface, with transcription being a necessary but secondary phenomenon mediated perhaps by communication between the cell membrane and the nucleus. Initial studies involving the inoculation of FLC lines 745A into syngeneic DBA2/J mice followed 1 wk later by the daily administration of the cryoprotective agent N-methylacetamide resulted in a significant and consistent inhibition of FLC proliferation in the spleens of treated mice and to a lesser extent the inhibition of leukemic cell proliferation in bone marrow. The induction of leukemic cell differentiation in vivo may provide a mode of therapy for leukemia. (29 Refs)

325. PHOSPHOLIPID MEMBRANE STABILIZATION BY DIMETHYLSULFOXIDE AND OTHER INDUCERS OF FRIEND LEUKEMIC CELL DIFFERENTIATION.

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Roswell Park Memorial Institute, 666 Elm Street, Buffalo, N.Y. 14263
Biochim Biophys Acta; 448(3):460-473 1976

A large number of low molecular weight polar cryoprotective agents have recently been found to induce erythroid differentiation of Friend leukemic cells in vitro. The effect of these agents on membrane fluidity in *phospholipid vesicles* was studied by determining the solid-to-liquid crystalline phase transition using differential scanning calorimetry. Some of the inducing agents studies were found to raise the normal transition temperature (Tc) by a few degrees. All of these agents were found to produce a separate transition at a much higher temperature. Changes in the head group of the phospholipid, the pH, the presence of divalent cations, and the addition of other membrane-active compounds were found to significantly influence the inducing agent's effects on the Tc of phospholipid membranes. The ability of the different agents to produce a new transition at a high temperature was found to correlate well with their ability to induce Friend leukemic cell differentiation. The possible mechanisms of action of the chemical inducers, and the significance of the observed membrane effects on differentiation and malignancy are discussed. It is concluded that inducing agents decrease the fluidity and stabilize phospholipid membranes, and that their effects in cell differentiation might be initiated by a similar change in the properties of cell membranes. (Author Abstract)

326. EFFECTS OF LOCAL ANESTHETICS ON MEMBRANE PROPERTIES. I. CHANGES IN THE FLUIDITY OF PHOSPHOLIPID BILAYERS.

Papahadjopoulos D, Jacobson K, Poste G, Shepherd G
Roswell Park Memorial Inst., Buffalo, N.Y. 14203
Biochim Biophys Acta; 394:504-518 1975

The effect of the local anesthetic dibucaine hydrochloride on the solid to liquid-crystalline phase transition in phospholipid vesicles was studied by calorimetry and fluorescence polarization. The partition coefficient (greater than 3,000) of dibucaine in the membranes of vesicles prepared from acidic phospholipid membranes was more than 20 times higher than in neutral phospholipid membranes under the same conditions. Calorimetric measurements on vesicles prepared from acid phospholipids (bovine brain phosphatidylserine, dipalmitoylphosphatidylglycerol) showed that dibucaine (1 x 10(-4) moles) significantly reduced the gel-liquid crystalline transition temperature (Tc). This fluidizing effect of dibucaine on acidic phospholipid membranes was even more marked in the presence of calcium ion. In contrast, dibucaine at the same conc did not alter the Tc of neutral phospholipids (dipalmitoylphosphatidylcholine). A significant increase in the fluidity of neutral phospholipid membranes occurred only at higher dibucaine conc (2 x 10(-3) moles). Measurements of the fluorescence polarization and lifetime of the probe, 1,6-diphenylhexatriene, in acidic phospholipid vesicles revealed that dibucaine (1 x 10(-4) moles) increased the probe rotation rate, the increase presumably corresponding to an increase in membrane fluidity. A good correlation was obtained between fluorescence polarization data on dibucaine-induced changes in membrane fluidity and calorimetric measures on vesicles of the same type. These results suggest that dibucaine might alter the binding and distribution of membrane proteins.

327. EFFECT OF BISCOCLAURIN ALKALOID ON THE CELL MEMBRANE RELATED TO MEMBRANE FLUIDITY.

Utsumi K, Miyahara M, Sugiyama K, Sasaki J
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Acta Histochem Cytochem; 9(1):59-68 1976

The effect of the biscoclaurin alkaloid, cepharanthin (CEP), on cell membrane fluidity is described. When *liposomes*, AH-130 ascites hepatoma cells, Ehrlich ascites tumor cells, and RBC were treated with lead acetate, lysolecithin, phospholipase A, and snake venom, CEP inhibited the release of potassium ions. However, CEP did not inhibit potassium ion release induced by hemagglutinin virus, ionophores, and Triton X-100. Furthermore, CEP inhibited cap formation of Ehrlich ascites tumor cells and rat monocytes, as well as the release of histamine from rat peritoneal mast cells. Spin-label studies and fluorescence polarization analyses indicated that CEP decreased the fluidity of cell membranes. It is concluded that the biscoclaurin alkaloid, CEP, acts as a significant membrane stabilizing agent and also decreases membrane fluidity. (27 refs)

B.

Use of liposomes to study membrane transport mechanisms

328. LACTATE TRANSPORT IN HUMAN ERYTHROCYTES AND ASCITES TUMOR CELLS AND ITS CONTROL BY INHIBITORS (MEETING ABSTRACT).

Dubinsky W, Belt J, Buschbaum R, Racker E
Biochemistry, Molecular and Cell Biology, Cornell Univ., Ithaca, NY, 14853
Fed Proc; 37(6):1532 1978

Lactate transport in ascites tumor cells is associated with the movement of protons. We find that lactate transport in human RBC takes place by a similar mechanism. Lactate analogues and several bioflavanoids inhibit lactate transport in human RBC and Ehrlich ascites cells. A new procedure was developed for the assay of lactate efflux based on the pronounced differences in pH optimum and temperature coefficients between glycolysis and lactate transport. Uptake was measured with radioactive lactate. Some striking differences were observed in the effectiveness of certain inhibitors depending on the direction of lactate flux suggesting an asymmetry of the transport mechanism. For example, quercetin at 0.2 microg per ml inhibited at comparable initial lactate concentrations efflux in ascites cells more strongly than influx. Quercetin was also more effective as an inhibitor of lactate efflux than of glycolysis resulting in the accumulation of lactate intracellularly. Crude membrane preparations from both RBC and ascites cells were incorporated into *liposomes* and an inhibitor-sensitive lactate transport was demonstrated.

329. RECONSTITUTION OF D-GLUCOSE TRANSPORT CATALYZED BY A PROTEIN FRACTION FROM HUMAN ERYTHROCYTES IN SONICATED LIPOSOMES (MEETING ABSTRACT).

Kasahara M, Hinkle PC
Section of Biochemistry, Molecular and Cell Biology,Cornell University, Ithaca, New York 14853
Proc Natl Acad Sci USA; 73(2):396-400 1976

A protein fraction was obtained from human erythrocyte ghosts by solubilization with Triton X-100 or octylglucoside. Triton X-100 was removed from the protein by Bio-Beads SM-2 and octylglucoside, by diafiltration. The solubilized protein fraction catalyzed D-glucose uptake when reconstituted in sonicated liposomes. The uptake was time dependent and inhibited by mercuric ions or cytochalasin B. The results indicate that the uptake represents transport of the sugar into the liposomes rather than binding to the reconstituted liposomes.

330. RECONSTRUCTION AND PURIFICATION OF THE D-GLUCOSE TRANSPORTER FROM HUMAN ERYTHROCYTES.

Kasahara M, Hinkle PC
Dept. Biochemistry, Public Health Res. Inst. City of New York, Inc., New York, NY 10016
J Biol Chem; 252(20):7384-7390 1977

The D-glucose transporter from human RBC was solubilized from washed membranes using Triton X-100. After removal of the Triton X-100 with Bio-Beads SM-2, the protein was incorporated into *phospholipid vesicles* by a sonication method but including a freeze-thaw step after adding the protein to the phospholipids. This modification improved reproducibility and increased the extent of D-glucose transport. Using the reconstitution of D-glucose transport as the assay, the component catalyzing transport was purified from the Triton extract by DEAE-cellulose chromatography. The active fraction contained one major protein (96%) with apparent mol wt (sodium dodecyl sulfate-polyacrylamide gel electrophoresis) of 55,000 dalton and a high lipid content. The protein stained with periodic acid-Schiff reagent, indicating that it is probably a glycoprotein. Antibody absorption indicated that the protein is exposed to the inner face of the RBC membrane. D-Glucose transport into liposomes reconstituted with the purified protein fraction was inhibited by mercuric ions or cytochalasin B, but not by phloretin or stilbestrol. The specific activity of D-glucose transport was 85 nanomol/min/mg of protein at 0.2 mM D-glucose, which is 10-fold higher than that of reconstituted liposomes with crude Triton extract. (Author abstract) (33 Refs)

331. BINDING OF CYTOCHALASIN B TO THE PURIFIED GLUCOSE TRANSPORTER FROM HUMAN ERYTHROCYTES (MEETING ABSTRACT).

Sogin DC, Hinkle PC
Dept. Biochem., Cornell Univ., Ithaca, NY, 14853
Fed Proc; 38(3,part1):245 1979

Cytochalasin B, a potent inhibitor of the D-glucose transport system in human erythrocytes, binds to the purified transporter with a dissociation constant of 0.15 uM and an extent of 11 nanomole/mg protein as determined by equilibrium dialysis using 3H-cytochalasin B. The extent suggests that one molecule of inhibitor is bound per two peptide chains of mol wt of 45,000 for the peptide chain alone. To accurately determine protein concentration, the 10-fold excess lipid by wt present in fractions of purified transporter was extracted with (CH3CH2)2O:CHCl3:CH3OH (6:2:1) after adding trichloroacetic acid to 5%, deoxycholate to 0.2 mg/ml and NaCl to 0.4 M to prevent extraction of the protein. The samples were hydrolyzed with NaOH at 110 C and total amino acids were determined by manual ninhydrin. Similar binding data were obtained for the transporter reconstituted in *liposomes*. The following compounds were linear competitive inhibitors of binding of cytochalasin B; D-glucose (K = 40 milliM), maltose (125 milliM), phloretin (25 uM), diethylstilbestrol (17 uM), 6.0-propyl-D-galactose (52 milliM), propyl beta-d-glucopyranoside (22 milliM), DL-dithiothreitol (0.93 milliM). (2 Refs)

332. PARTIAL PURIFICATION AND RECONSTITUTION OF NEUTRAL AMINO ACID TRANSPORT COMPONENTS FROM EHRLICH ASCITES TUMOR CELLS (MEETING ABSTRACT).

Cecchini G, Payne GS, Oxender DL
The Univ of Michigan, Ann Arbor, Mi 48109
Fed Proc; 36(3):804 1977

Plasma membranes enriched 25-fold based upon Na+ + K+ ATPase activity have been prepared from Ehrlich ascites tumor cells. Solubilized protein fractions have been obtained from the plasma membranes either by extraction with 0.5% Triton X-100 or by extraction with 2% cholate. Partial purification of the solubilized protein fraction has been obtained by utilizing a combination of ammonium sulfate precipitations and column chromatography. Leucine binding activity has been detected in the Triton X-100 solubilized plasma membrane fraction. The leucine binding activity was measured by equilibrium dialysis and is saturable with high levels of leucine or phenylalanine and is only partially saturable by alanine. These properties are similar to those previously identified as the L system. The cholate extracted plasma membrane fraction was incorporated into *liposomes* by addition to sonicated liposomes or by dialysis against potassium phosphate buffer in the presence of phospholipids. Lipids composed of a 4:1 ratio of phosphatidylcholine to phosphatidylethanolamine or a mixture of soybean phospholipids were used for formation of the liposomes. Time dependent transport for alanine or leucine could be demonstrated in the liposomes when energy was supplied as a membrane potential produced by valinomycin mediated K+-diffusion. (Author Abstract)

333. INTERACTION OF SMALL MOLECULES WITH PHOSPHOLIPID BILAYERS. BINDING TO EGG PHOSPHATIDYLCHOLINE OF SOME UNCHARGED MOLECULES (2-ACETYLAMINOFLUORENE, 4-DIMETHYLAMINOAZOBENZENE, OESTRONE AND TESTOSTERONE) THAT BIND TO LIGANDIN AND AMINOAZO-DYE-BINDING PROTEIN A.

Tipping E, Ketterer B, Christodoulides L
Freshwater Biological Assoc., Ferry House, Ambleside, Cumbria LA22 0LP, England
Biochem J; 180(2):319-326 1979

The possible involvement of ligandin and aminoazo dye-binding protein A in intracellular transport was assessed by determining how their ligands, most of which are molecules with hydrophobic moieties, interact with cellular membranes. To obtain this information, the interactions of 2-acetylaminofluorene (AAF), 4-dimethylaminoazobenzene (DAB), estrone, and testosterone with aqueous dispersions of egg phosphatidylcholine and egg phosphatidylcholine/cholesterol (1:1 molar ratio) were examined by equilibrium dialysis and spectrophotometry. At 25 C and pH 7.4, the partition coefficients for binding to phosphatidylcholine [expressed as (mol of ligand bound/mol phosphatidylcholine)/unbound ligand concentration] were 5.0 x 10(3), 2.1 x 10(4),

3.1 x 10(3), and 4.2 x 10(2) liters/mole for AAF, DAB, estrone, and testosterone, respectively. In the ranges studied, these values were independent of concentration. The introduction of cholesterol into the lipid bilayers caused large decreases in the partition coefficients of estrone and testosterone, but had relatively little effect on the binding of AAF and DAB. By assuming that the interactions with egg phosphatidylcholine bilayers resemble those with the phospholipid components of mammalian intracellular membranes, the phosphatidylcholine partition coefficients, together with data for binding to the intracellular proteins ligandin and aminoazo dye-binding protein A, enable the subcellular distributions of the four components to be estimated. For the rat hepatocyte, up to 98%, 99%, 89%, and 58% of the total AAF, DAB, estrone and testosterone may be membrane-bound, respectively. (34 Refs)

334. INTERACTIONS OF SMALL MOLECULES WITH PHOSPHOLIPID BILAYERS: BINDING TO EGG PHOSPHATIDYLCHOLINE OF SOME ORGANIC ANIONS (BROMOSULPHOPHTHALEIN, OESTRONE SULPHATE, HAEM AND BILIRUBIN) THAT BIND TO LIGANDIN AND AMINOAZO-DYE-BINDING PROTEIN A.

Tipping E, Ketterer B, Christodoulides L
Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London, England
Biochem J; 180(2):327-337 1979

To assess the possible involvement of ligandin and aminoazo-dye-binding protein A in intracellular transport it is necessary to know how their ligands, most of which are molecules with hydrophobic moieties, interact with cellular membranes. To obtain such information we examined the interactions of bromosulfophthalein, estrone sulfate, heme and bilirubin with aqueous dispersions of egg phosphatidylcholine and egg phosphatidylcholine/cholesterol (1:1, M ratio) by equilibrium dialysis and spectrophotometry. In all four cases, saturation effects were observed. Values of Vmax (V = mole of compound bound/mole of lipid phosphorus) at 25 C were: for bromosulfophthalein, approx 0.1; for estrone sulfate, approx 0.25; for heme, approx 0.25 (all at pH 7.4); and for bilirubin 0.1-0.2 (at pH 8.2). Limiting values of V/c (c = unbound concentration) as V approaches 0 at 25 C and pH 7.4 are: for bromosulfophthalein, 6.25 x 10(4) liters/mole; for estrone sulfate, 7.8 x 10(2) liters/mole; for heme, 4.5 x 10(5) liters/mole and for bilirubin, 1.2 x 10(4) liters/mole. For heme the result depends on the assumption that only the monomeric form binds to the lipid. The binding of each compound was decreased by cholesterol; bromosulfophthalein and estrone sulfate were affected more than heme and bilirubin. Bromosulfophthalein at saturating concentration decreased the limiting values of V/c of the other three compounds by approx one order of magnitude. By assuming that the interactions with egg phosphatidylcholine resemble those with the phospholipid components of mammalian intracellular membranes the binding data for phosphatidylcholine, together with data for binding to the intracellular proteins ligandin and aminoazo-dye-binding protein A, enable the subcellular distributions of the four compounds to be estimated. For the rat hepatocyte up to 92, 51, 98 and 47% of the total bromosulfophthalein, estrone sulfate, heme and bilirubin respectively may be membrane-bound. (Author abstract) (24 Refs)

335. INTERACTIONS OF AN HOMOLOGOUS SERIES OF CARBAMATES WITH PHOSPHATIDYLCHOLINE LIPOSOMES.

Wood SG, Symons AM, Bridges JW
Huntingdon Res. Centre, Huntingdon PE18 6ES, England
Biochem Pharmacol; 28(3):393-395 1979

In an attempt to ascertain how membrane composition influences the passive intestinal absorption of an homologous series of aliphatic carbamates, permeability of these compounds into a model membrane system of phosphatidylcholine liposomes has been investigated. The leakage of 22Na+ previously incorporated into these microvesicles has been measured to establish effects on permeability. All the carbamates were found to destabilize the liposomes at a concentration of 10(-3) M, as indicated by increased permeability of the membranes to cation. This destabilization was not linearly related to the partition coefficients of the carbamates. It was found that the increasing destabilization produced by the carbamates as the homologous series was ascended was due to increased incorporation of the carbamates into the liposome membrane. (Author abstract) (7 Refs)

336. PHOSPHORYLATION OF THE BETA SUBUNIT OF NA+K+-ATPASE IN EHRLICH ASCITES TUMOR BY A MEMBRANE-BOUND PROTEIN KINASE.

Spector M, O'Neal S, Racker E
Section Biochemistry, Molecular and Cell Biology, Div. Biological Sciences, Cornell Univ., Ithaca, NY, 14853
J Biol Chem; 255(18):8370-8373 1980

We have shown previously that proteoliposomes reconstituted with purified Na+K+-ATPase from Ehrlich ascites tumor cells transport Na+ with low efficiency. We now present evidence that this low efficiency (expressed in the ratio of Na+-transported/ATP-hydrolyzed) is caused by the phosphorylation of the beta subunit of the Na+K+-ATPase by an endogenous protein kinase. On addition of [gamma-32P]ATP, crude tumor plasma membrane preparations phosphorylated the beta subunit of the ATPase, whereas crude mouse brain plasma membranes did not. However, solubilized Na+K+-ATPase from either tumor or brain were phosphorylated by purified protein kinase from the tumor plasma membrane and dephosphorylated by a phosphatase. In both cases, the phosphorylated enzyme was inefficient; the dephosphorylated enzyme was efficient after reconstitution into liposomes. During isolation of the Na+K+-ATPase from Ehrlich ascites tumor or mouse brain, an endogenous protease partially cleaved from the beta subunit a polypeptide of 29,000 daltons that contained the phosphorylation site. The proteolytic cleavage of the beta subunit was partially inhibited by phenylmethylsulfonyl fluoride and the major site of phosphorylation was then seen in the 53,000-dalton beta subunit of the enzyme. The isolated 29,000-dalton polypeptide from mouse brain ATPase was phosphorylated by tumor protein kinase with a stoichiometry of 1 mol of phosphate/mol of protein. When this 29,000-dalton polypeptide from mouse brain was incorporated into the tumor Na+K+-ATPase after mild proteolytic digestion, a marked increase in efficiency was observed after reconstitution of the Na+ pump. (Author abstract) (12 Refs)

337. LATERAL COMPRESSIBILITY OF LIPID MONO- AND BILAYERS THEORY OF MEMBRANE PERMEABILITY.

Nagle JF, Scott HL
Dept. Physics, Carnegie-Mellon Univ., Pittsburgh, PA, 15213
Biochim Biophys Acta; 513(2):236-243 1978

The passive sodium permeability of pure lipid vesicles and dispersions has a large peak at the bilayer phase transition temperature. We discuss this anomaly in terms of density fluctuations, which can open up cavities in the headgroup region into which small ions can enter, and which may be large if bilayer conditions at the melting point are similar to those near the critical point which seems to exist in monolayers. We present two arguments, one thermodynamic and one microscopic, which suggest that the permeability is proportional to the lateral compressibility. We then calculate the lateral compressibility for two previously published theoretical models and compare the results with experiments. (Author abstract) (20 Refs)

338. RECONSTITUTION OF AN ATP-DEPENDENT SODIUM PUMP WITH AN ATPASE FROM ELECTRIC EEL AND PURE PHOSPHOLIPIDS.

Racker E, Fisher LW
Section Biochemistry, Molecular-Cell Biology, Cornell Univ., Ithaca, NY 14853
Biochem Biophys Res Commun; 67(3):1144-1150 1975

An ATP-dependent sodium pump was reconstituted with an ATPase preparation from the electric eel and purified phospholipids. Vesicles reconstituted by the sonication procedure catalyzed Na+ translocation at a rate 10-20 times higher than vesicles reconstituted by the cholate-dialysis procedure. A small but reproducible stimulation of Na+ transport by valinomycin in the presence of K+ was observed. The effect of phospholipid composition, of ionophores, and of ouabain on Na+ translocation was investigated, as well as the effect of ionophores and inhibitors on the reconstituted Na+ pump. The determination of the possible involvement of a proteolipid in the operation of the Na+ pump requires further resolution of the Na+/K+ ATPase preparation. This problem is of interest in view of the demonstration of an inefficient Na+/K+ pump in Erlich ascites tumor cells.

339. CA++ TRANSLOCATION IN EHRLICH ASCITES TUMOR CELLS.

Hinnen R, Miyamoto H, Racker E
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J Membr Biol; 49(4):309-324 1979

Ca++ uptake into Ehrlich ascites tumor cells was studied at 0 C in the presence of mitochondrial inhibitors, conditions that minimized complications caused by sequestration of Ca++ into organelles or by excretion. Under these conditions Ruthenium Red inhibited Ca++ uptake, but other previously implicated ions, such as Pi or Mg++, had no effect. Valinomycin either inhibited or slightly stimulated Ca++ uptake depending on the presence of excess K+ on the outside or inside of the cell, respectively. Nigericin inhibited Ca++ transport. Based on these data we propose an electrogenic uptake of Ca++ possibly via a Ca++/H+ antiport mechanism. The observation that glucose inhibited Ca++ uptake suggested that in Ehrlich ascites tumor cells an energy-driven Ca++ expulsion mechanism is operative, similar to that in RBC. Plasma membrane preparations of ascites tumor cells were found to contain a Ca++-dependent ATPase. These preparations, when incorporated into *liposomes* in an inside-out orientation, catalyzed an ATP-dependent uptake of Ca++. (Author abstract) (23 Refs)

340. A COUPLING FACTOR FROM SARCOPLASMIC RETICULUM REQUIRED FOR THE TRANSLOCATION OF CA+ IONS IN A RECONSTITUTED CA+ATPASE PUMP.

Racker E, Eytan E
Section Of Biochemistry, Molecular and Cell Biology, Cornell University, Ithaca, New York 14853
J Biol Chem; 250(18):7533-7534 1975

During purification of the Ca+ATPase from sarcoplasmic reticulum of rabbit muscle, different fractions with similar Ca+ATPase activity were found to vary greatly in their ability to catalyze Ca+ translocation in reconstituted *liposomal systems.* A heat-stable fraction isolated from the fraction most active in Ca+ translocation enhanced several-fold the Ca+ translocation rate of the least active fraction. It also increased the ratio of Ca+ translocation to ATP hydrolysis over 5-fold. The properties of the coupling factor resemble those of the proteolipid previously described by MacLennan et al (MacLennan, D H, Yip, C C, Iles, G H, and Seaman, P (1972) Cold Spring Harbor Symp Quant Biol 37, 469-478). When the heat-stable factor was added to either sarcoplasmic reticulum fragments or to liposomes after, rather than before, reconstitution, it acted as an ionophore abolishing Ca+ translocation. (Author Abstract)

341. FLUXES OF CA2+ AND CONCEPTS (MEETING ABSTRACT).

Racker E
Section Biochemistry, Cornell Univ., Ithaca, NY, 14853
Fed Proc; 38(3,part1):304 1979

The transport of Ca2+ into cells is an important process which is difficult to analyze because, soon after entry Ca2+ is either pumped out of the cell or pumped into intracellular organelles. We have studied Ca2+ uptake into Ehrlich ascites tumor cells at 0 C in the presence of antimycin and oligomycin, conditions that minimize secondary movements. The transport of Ca2+ through the plasma membrane is electrogenic and can be influenced (inhibited or stimulated) by imposing (with K+ and valinomycin) an artificial voltage clamp across the membrane. The Ca2+ ATPases of the plasma membrane from pig RBC and Ehrlich ascites tumor cells have been reconstituted into *liposomes.* The regulator (modulator) protein stimulates Ca2+ uptake via the RBC enzyme but not (under the same conditions) via the tumor enzyme. Sarcoplasmic reticulum (SR) contains several proteolipids. After reconstitution, two of these catalyzed Ca2+, Rb+ and Na+ transport. Their possible role in SR function will be discussed. Dicyclohexylcarbodiimide (DCCD) is a potent inhibitor of SR-ATPase provided all Ca2+ is removed from the membrane. This is achieved by treatment with EGTA in the presence of A-23187. One mole of bound 14C-DCCD per 4 moles of enzyme inhibits activity suggesting that the active unit is a tetramer. Based on studies of net ATP formation from ADP and Pi, we propose a model for the SR-ATPase mode of action in which the key reaction is the displacement of Mg2+ by the Ca2+ gradient. (1 Ref)

C.

Liposomes as models of viral membranes

342. TRANSLOCATION OF A HYDROCARBON FLUORESCENT PROBE BETWEEN EPSTEIN-BARR VIRUS AND LYMPHOID CELLS: AN ASSAY FOR EARLY EVENTS IN VIRAL INFECTION.

Rosenthal KS, Yanovich S, Inbar M, Strominger JL
Harvard Medical Sch., Boston, MA, 02115
Proc Natl Acad Sci USA; 75(10):5076-5080 1978

An assay to determine early biochemical events during cell-virus interactions is described, as well as its application in measuring events following the interaction of Epstein-Barr virus (EBV) with different types of lymphoid cells. The method is based on translocation of the hydrocarbon fluorescent probe dephenylhexatriene (DPH) between viral envelopes and cellular membranes, as monitored by fluoresecence polarization (P) analysis. Using a model system, the high P value (0.324) of DPH-labeled cholesterol/phosphatidylcholine *liposomes* and the low P value (0.157) of DPH-labeled phosphatidylcholine liposomes allowed detection of DPH-translocation between interacting liposomes. This was monitored by the change in P in either direction. The P value of DPH-labeled EBV was significantly higher (p.350-0.392) than the P value of DPH-labeled lymphoid cells (0.238-0.289). Hence, DPH translocation could be detected by changes in P following incubation of DPH-labeled EBV and nonlabeled cells. A marked decrease in P was observed after incubation of DPH-labeled EBV with nonlabeled lymphoblastoid Raji cells or fresh human B lymphocytes. However, only a slight decrease in P was obtained when DPH-labeled EBV was incubated with nonlabeled fresh human T lymphocytes or fresh rabbit T or B lymphocytes. Moreover, incubation of human B lymphocytes with purified complement 3 (a putative inhibitor for the EBV receptor) prior to the addition of DPH-labeled EBV abolished the decrease in the P value. Most of these experiments were carried out with both the P3HR-1 and B95-8 EBV strains. Therefore, DPH translocation, as determined by fluorescence polarization, measures some early event during interaction of this enveloped virus and mammalian cells. The potential applicability of this technique to other viruses is illustrated by an experiment with Semliki Forest virus. (32 Refs)

343. VIRAL MEMBRANES: MODEL SYSTEMS FOR STUDYING BIOLOGICAL MEMBRANES.

Patzer EJ, Wagner RR, Dubovi EJ
Dept. Biochemistry, Stanford Univ., Stanford, CA
CRC Crit Rev Biochem; 6(2):165-217 1979

The membranes of enveloped viruses have been found to provide ideal systems for studies of the chemical structure, organization, physical properties, and certain functions of biological membranes. This review focuses attention on the simple enveloped viruses, which contain only two to four membrane-associated protein species and can be produced in large amounts that are readily purified to homogeneity. Although closely related and interdependent, viral membrane lipids and proteins are discussed in separate sections and, where appropriate, compared with cell membrane and *liposomes*. Viral membrane lipids are analyzed from the standpoint of their cellular origin, composition, bilayer orientation of phospholipids, cholesterol and glycolipids, and dynamic properties studied by biophysical membrane probes. Also discussed in some detail are the role of viral proteins in selecting specific membrane lipids, selective perturbation of lipids by specific lipases and polyene antibiotics, and virion lipid depletion or exchange by interaction with lipid vesicles or by varying growth conditions. The viral membrane glycoproteins are discussed from the standpoint of their amphipathic nature, transmembrane location, synthesis in cells and cell-free systems, carbohydrates and glycosylation, assembly with membranes, and their function in host cell recognition and as membrane fusion factors. The sparser literature on the nonglycosylated matrix (M) proteins is analyzed in terms of their role in membrane organization, assembly with nucleocapsid, and their spatial relationship to the glycoproteins. Interaction of virion membranes with host cell membrane surfaces is discussed briefly. (Author abstract) (358 Refs)

344. RECONSTITUTION OF MEMBRANES WITH INDIVIDUAL PARAMYXOVIRUS GLYCOPROTEINS AND PHOSPHOLIPID IN CHOLATE SOLUTION.

Hsu MC, Scheid A, Choppin PW
Rockefeller Univ., New York, NY, 10021
Virology; 95(2):476-491 1979

A method for reconstituting biologically active membranes with individual Sendai virus glycoproteins (HN and F) and phosphatidylcholine is described. The glycoproteins were isolated in the presence of Triton X-100 and transferred into cholate soln by sedimentation into a sucrose gradient containing 2% cholate. The membranes were then reconstituted with HN or F and phosphatidylcholine by removal of the cholate through the use of dialysis. Experiments with radioactively labeled detergents showed that the removal of Triton X-100 by sedimentation into cholate and the removal of cholate by dialysis were essentially complete. With the F protein, vesicles 400-800 A in diameter and filaments 600-800 A long were formed, depending on the proportions of lipid and protein in the initial mixture. Both structures were covered with glycoprotein spikes. With the HN protein, only vesicles were formed, and the densities of the spikes on the surface were dependent on the initial lipid to protein ratio. Membranes reconstituted from HN protein exhibited hemagglutinating and neuraminidase activities. Reconstituted particles containing the F protein exhibited hemolytic activity when a mechanism was provided to attach the F protein-lipid complex to the cell; ie, by the addition of wheat germ agglutinin. These results confirm the role of F protein in membrane fusion and show that the requirements for F protein activity are the previously demonstrated proteolytic processing of F, the insertion of F protein into lipid, and the presence of an attachment mechanism. (34 Refs)

345. INTERACTION OF VESICULAR STOMATITIS VIRUS WITH LIPID VESICLES: DEPLETION OF CHOLESTEROL AND EFFECT ON VIRION MEMBRANE FLUIDITY AND INFECTIVITY.

Moore NF, Patzer EJ, Shaw JM, Thompson TE, Wagner RR
Natural Environment Res. Council, Unit Invertebrate Virology, Oxford, England OX1 3UB
J Virol; 27(2):320-329 1978

Interaction with excess unilamellar phosphatidylcholine (PC) vesicles resulted in depletion of as much as 90% of the cholesterol from the membrane of intact vesicular stomatitis (VS) virus. The cholesterol depletion was not significantly influenced by the proteolytic removal of virion glycoprotein spikes, but it was temperature dependent. Cholesterol depletion caused substantial reduction in anisotropy of the VS virion membrane as measured by fluorescence depolarization of the lipophilic probe 1,6-diphenyl-1,3,5-hexatriene; residual adsorbed vesicles represent a significant factor in this apparent increase in virion membrane fluidity. Interaction with PC vesicles resulted in a substantial loss of VS viral infectivity as measured by plating efficiency on L-cell monolayers. Reduction in infectivity appeared to be related to temperature-dependent depletion of virion cholesterol by PC vesicles. Interaction of VS virions with cholesterol-con-

taining PC vesicles resulted in significantly less decline in infectivity, but attempts to restore cholesterol and infectivity to depleted VS virions were unsuccessful. Depletion of virion cholesterol apparently results through collision with PC vesicles rather than movement of cholesterol monomers or micelles through the aqueous phase, because PC vesicle-virion interaction in the presence of cholesterol oxidase did not result in substantial oxidation of translocated cholesterol. (Author abstract) (35 Refs)

346. RECONSTITUTION INTO LIPOSOMES OF THE GLYCOPROTEIN OF VESICULAR STOMATITIS VIRUS BY DETERGENT DIALYSIS.

Petri WA, Wagner RR
Dept. Microbiology, Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
J Biol Chem; 254(11):4313-4316 1979

The glycoprotein of vesicular stomatitis virus (VSV) was selectively liberated from the virion membrane by the dialyzable nonionic detergent beta-D-octylglucoside. When mixtures of viral glycoprotein and egg lecithin were dialyzed free of octylglucoside, glycoprotein vesicles with spikes protruding in the same external orientation as the VSV membrane formed spontaneously. Evidence for a similar insertion and orientation VSV glycoprotein in both phosphatidylcholine vesicles and the virion membrane was obtained. (19 Refs)

347. PERMEABILITY PROPERTIES OF THE MEMBRANE OF VESICULAR STOMATITIS VIRIONS.

Bittman R, Majuk Z, Honig DS, Compans RW, Lenard J
Dept. Chemistry, Queens Coll. City of New York, Flushing, NY 11367
Biochim Biophys Acta; 433(1):63-74 1976

The osmotic permeability properties of lipid-containing virus particles was compared with other biological membranes and with *artifical lipid membranes.* Observations of the light-scattering properties of several enveloped viruses indicated that virions (vesicular stomatitis, SV5 and influenza) are osmotically active, responding to NaCl gradients by swelling in hypo-osmolar solutions and shrinking in hyperosmolar solutions. These observations indicated a direct rather than an inverse proportionality between volume change and absorbance change. This is probably due to the fact that absorbance increases as the particle shrinks, but corrections must be made for mass, size, shape, refractive index and volume of the particle. The permeability barrier responsible for this osmotic response in vesicular stomatitis virions was modified both by protease treatment to remove the viral glycoprotein and by treatment with the polyene antibiotic filipin; this agent is known to interact with cholesterol in liposomes and membranes. Filipin altered the kinetic and equilibrium permeability behavior of virions but the extent of leakage of osmotic shocking agent was less than that in lecithin/cholesterol and lecithin/ergosterol liposomes and in ergosterol-containing ciliary membranes. Negative-staining electron microscopy revealed that filipin treatment caused structural changes in the viral membrane. Intact virions exhibited appreciably larger responses to osmotic change than did protease-treated virus particles.

X. REVIEWS AND GENERAL ARTICLES ON LIPOSOMES

348. PROPERTIES AND BIOLOGICAL EFFECTS OF LIPOSOMES AND THEIR USES IN PHARMACOLOGY AND TOXICOLOGY.

Kimelberg HK, Mayhew EG
Div. Neurosurgery, Albany Medical Coll., Union Univ., Albany, NY
CRC Crit Rev Toxicol; 6(1):25-79 1978

Properties of liposomes are discussed in relation to their ability to serve as carriers for drugs such as anticancer agents in vivo. Limited antitumor studies indicate that some drugs may be more effective, have the same activity, or be less active when entrapped in liposomes. Independent reports from two laboratories have shown that entrapped actinomycin D increases the life span of tumor-bearing mice against two different tumors (Ehrlich ascites carcinoma and AKR-A ascites tumor). Entrapped actinomycin D has also been shown to be less toxic than the free drug, with the reduction in toxicity being related to a reduction in the immunosuppressive effects of drug. Single doses of liposome-entrapped cytosine arabinoside have been shown to be quite effective against both ip (ascites) and iv (disseminated) L1210 leukemia. Liposome entrapment has not been found to increase the effectiveness of methotrexate against ascitic L1210 tumor that is sensitive to the free drug. Moreover, the entrapped drug was more toxic than the free drug after ip injection. Although up to 10-fold higher levels of the intact entrapped drug as compared with the free drug are obtained in plasma, proportionally much less of the entrapped drug is available to the L1210 cells. Also, more of the drug seems to be available for some normal tissues as judged by the toxic reactions of entrapped methotrexate. Liposome entrapment of nitrogen mustard has been reported to increase the drug's activity against L1210 cells and Ehrlich ascites tumors. In tests against 6C3HED lymphoma, liposome entrapment of asparaginase has been found to abolish allergic reactions to the drug, although there was no evidence that liposome entrapment potentiated antitumor activity. The above studies are essentially preliminary survey experiments in which the tumor system was not selected to achieve max effects based on concepts of the mode of action of liposome-entrapped drugs. (220 Refs)

349. LIPOSOMES - METHODOLOGY AND APPLICATIONS. (PP. 549-574)

Ryman BE, Tyrrell DA
Dept. Biochemistry, Charing Cross Hosp. Medical Sch., London, England
Lysosomes in Applied Biology and Therapeutics Vol. 6. Dingle JT, Jacques PJ, Shaw IH, ed. Amsterdam, North-Holland Publishing Co., Frontiers of Biology, Vol. 48, 719 pp., 1979.

Methodology available for entrapment of therapeutic agents within liposomes is reviewed, and potential applications of liposome carriers are described. Methodology is discussed with respect to various methods of preparing liposomes, liposome nomenclature, lipid composition of liposomes, entrapment of materials in liposomes, separation of non-entrapped materials from liposomes, nature of entrapment, quantitation of entrapment, leakage of entrapped materials, and sterile preparations of liposomes. Liposomes as proposed carriers for enzymes, chelating agents, drugs, hormones, and other substances are considered. Specific antitumor drugs that have been entrapped in liposomes are listed. Results are noted which suggest that antitumor drug admin-

istration in liposomes may or may not increase the effectiveness in particular animal systems; there is little evidence of an increase in the therapeutic indexes of these drugs. Clinical applications and uses in various model animal tumor systems are discussed. The potential use of liposomes labeled with gamma-emitting substances to differentiate lymph nodes involved in metastatic spread from those that are unaffected is described. Other drugs that have been studied in their liposomally-entrapped form include penicillin G, polyinosinic acid:polycytidylic acid, vitamins A and K, histamine, sodium salicylate, dibucaine, tetracaine, glutathione, and colchicine. (200 Refs)

350. LIPOSOMES: STRUCTURE, PROPERTIES. EXAMPLES OF APPLICATIONS IN BIOLOGY AND MEDICINE.

Delattre J
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J Fr Biophys Med Nucl; 3(1):3-12 1979

Methods for the preparation of multilamellar and unilamellar liposomes are presented, and their potential use as drug carriers is discussed. Liposomes can be prepared to include a variety of compounds (enzymes, drugs, metabolites) and, in vivo, show a strong affinity for the reticuloendothelial system. Tumor cells incorporate liposomes at a higher rate than normal cells. Liposomes carrying actinomycin D and methotrexate have been successfully used in experiments with tumor-bearing mice. (94 Refs)

351. LIPOSOMES: THE MOLECULAR VEHICLE.

Debelfort A
No affiliation given
Recherche; 7(65):272-275 1976

Medical research indicates that liposomes hold great promise for the correction of enzyme deficits, the isolation and destruction of tumors and the production of vaccines. The brief history of liposomes is reviewed. Liposomes are double membranes of lipids separated by water compartments. Generally, they are produced from dehydrated phospholipids to which are added constituents, the drugs or enzymes which are to be carried in the bloodstream. These constituents then may travel without any degradation. Once the liposomes have been engulfed by the cells and ingested by the vacuoles that merge with the lysosomes, these constituents are released, and thus may act at a cellular level. Liposomes are used to contain substances that might otherwise react with the blood components, become degraded, or exert a general action. Since enzymes which are contained in liposomes still remain active, liposome transport may be used to correct enzyme deficits such as phenylketonuria, or galactosemia. Some, containing asparaginase, may be injected in pts with leukemia since the release of asparagine is accompanied by an improvement in the illness. The liposome may also aid in chemotherapy. The loading of liposomes with antimetabolites (5-FU, actinomycin D) has already resulted in ILS for some cancer-bearing mice. Liposomes could also act as tumor scanners. Once the fixation of antibodies on the liposomes is possible, liposomes containing anti-mitotic agents would serve as a weapon against tumor cells. Another application of liposomes concerns the preparation of vaccines, since they can be used as components able to increase the body's immune response. In this case, they are called virosomes. Vaccines carried by liposomes appear to confer an immunity greater than the one induced by a vaccine alone and they appear to have no side effects, such as allergies or fever. (9 refs)

352. MEMBRANE BIOLOGY AND CANCER THERAPY.

Wallach DF
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Pathobiol Annu; 8:189-216 1978

Membrane dysfunctions account for at least some of the critical anomalies that characterize malignant cells. Intersections between membrane biology and tumor therapy are discussed. Chemotherapy is directed primarily at the nucleus, but cell surface permeability to antitumor agents is often limited. Some resistant tumors are carrier-deficient or poorly permeable variants of wild-type cells. Broaching this membrane barrier is a major problem in chemotherapy. A promising application of membrane biology is targeting antitumor agents to tumor cells according to the surface properties of these cells. Some agents act on membrane targets, such as lysosomes (adriamycin or daunomycin complexes with DNA or other substances) or *liposomes* (methotrexate, cytosine arabinoside, or actinomycin D). Radiotherapy (RT) acts primarily at the nuclear level, but some cells (particularly certain lymphocytes) have radiosensitive plasma membrane sites. This may be relevant to the treatment of lymphoid malignancies and the possible adverse effects of RT on immunity. The efficacy of immunotherapy depends on the presence of cells capable of killing target tumor cells with certain surface membrane antigens. Progress in immunotherapy is expected with the further characterization and modification of tumor transplantation antigens. Hyperthermia, presently used as an adjunct to other treatments, seems to act primarily on cell membranes. It definitely affects the plasma membranes and may also act on mitochondria, lysosomes, and endoplasmic reticulum. The potential of thermotherapy may reside in the rational exploitation of membrane thermotropism. (139 Refs)

353. POTENTIAL OF LIPOSOMES AS DRUG-CARRIERS IN CANCER CHEMOTHERAPY: A REVIEW.

Kaye SB, Richardson VJ
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Cancer Chemother Pharm; 3(2):81-85 1979

Liposomes have been proposed as vehicles for the selective delivery of cytotoxic agents into tumor cells. Methotrexate, cytosine arabinoside, 5-fluorouracil, L-asparaginase, 6-mercaptopurine, 8-azaguanine, melphalan, nitrogen mustard, and BCNU are entrapped in the aqueous phase of the liposome structure; daunomycin, cis-diamminedichloroplatinum(II), vinblastine, and bleomycin in the lipid phase; and actinomycin D into both phases. In vitro and in vivo experiments have indicated an increase in the activity of antitumor agents and their active metabolites after liposome encapsulation, particularly for the treatment of resistant tumors. Liposome entrapment affects the tissue distribution and rates of clearance of cytotoxic agents; it also reduces their toxicity in most cases. No substantial degree of selective localization of liposomes in tumors has yet been achieved. In animals and cancer patients, the spleen and liver are consistently the major sites of uptake after iv administration of liposome-encapsulated agents. Some localization of liposomal labels in the vicinity of experimental animal tumors has been observed under certain circumstances. Further modifications (especially, incorporation of more specific tumor-associated antibody) may be more successful in achieving preferential tumor uptake. Much experimental work is needed before clinical application of liposome-encapsulated antitumor agents can be considered. (51 Refs)

354. THERAPEUTIC APPLICATIONS OF A MEMBRANE MODEL: THE LIPOSOME.

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Instituto de Biologia Celular, Universidad de Buenos Aires, Paraquay 2155, 1121 Buenos Aires, Argentina
Medicina (B Aires); 38(4):444-449 1978

Studies on the liposome as a possible vehicle of various drugs are reviewed. Liposomes, which are composed of lipid suspension in aqueous soln, are an ideal vehicle for drugs; the drugs are protected from the attack of enzymes, the vehicle is nontoxic and biodegradable, and liposomes do not form antibodies. A liposome is able to penetrate into cells, and the drug it carries can exert its effect at the lysosomal level. The drug is able to reach areas unaccessible to a free drug, and the dose can be reduced, which is especially important in the case of toxic drugs. Liposomes were successfully used experimentally as a vehicle for actinomycin D for iv injection. (16 Refs)

355. LIPOSOMES AS DRUG CARRIERS.

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Dept. Chemistry, Texas A and M Univ., College Station, TX 77842
Lif Sci; 20(7):1109-1120 1977

A review is provided of the use of liposomes as drug carriers, with brief descriptions of the structure and properties of liposomes, the method of drug entrapment, and proposed mechanisms for liposome-mediated drug deliveries. Information on in vivo and in vitro liposome-mediated drug deliveries is also surveyed. Both hydrophobic and polar drugs can be entrapped, the former dissolved in chloroform along with the lipid and cholesterol and the latter dissolved in aqueous buffers used in the liposome formation. Percentages of drug entrapment range from 0.10% to 60% for different drugs. Efficiency of drug encrapment depends on a number of parameters: volume of aqueous space within the liposome, drug solubility, solution pH, amount of cholesterol, sonication time, and presence of charged cosolubilizates. Retainment of trapped solutes is greatly influenced by the physical state of the liposome, and the distribution of the liposome encapsulated drug depends on the size and surface change of the liposome, as well as on the type of drug. The proposed mechanisms for drug release involve endocytosis and fusion, with the vesicle's state (fluidity and charge), rather than size, determining the mechanism of liposome incorporation into target cells. Beneficial effects of liposomes as drug carriers include reduced dosages, allergic and immunological reactions, increased cellular permeability, and delayed drug elimination. Some of the in vivo uses of liposomes include penicillin and actinomycin D (A-D) in rats; A-D in tumor-bearing mice; A-D and fluorouracil injected into rat testis; methotrexate injected into human hepatic artery and iv into monkeys; diphtheria toxoid in mice; asparaginase in rats; neuraminidase in rats; albumin and beta-fructofuranoxidase in rats; bleomycin (BL) in mice; BL, glucose oxidase, insulin, polyvinylpyrrolidone; 8-azaguanine in tumor-bearing mice; EDTA in rats and mice; EDTA and DTPA in mice; poly I, poly C in mice; insulin in rats; and 1-beta -D- arabinofuranosylcytosine 5'-triphosphate in tumor-bearing mice. Liposomes have provided a means of reducing drug losses and undesirable side effects, but liposome distribution is not very selective. Both chemical and biochemical modifications are being examined in order to increase selectivity. (97 Refs)

356. THE DRUG-CARRIER POTENTIAL OF LIPOSOMES IN CANCER CHEMOTHERAPY.

Gregoriadis G
Cancer Chemotherapy I. Hellmann K, Connors TA, ed. New York, Plenum Press, Chemotherapy, vol. 7, 1976.

The potential of liposomes for transporting anticancer agents to specific sites of action is discussed. In vitro and in vivo experiments indicate that liposomes can enter malignant cells. The iv or ia administration of liposome-entrapped radiolabeled albumin was followed by the localization of radioactivity in tumor cells, and in most instances uptake by tumors was higher than by surrounding normal tissue. Similar observations were made with a number of transplanted carcinomas in mice and rats that received liposomes containing In-labeled bleomycin. One difficulty impeding the potential use of liposomes as anticancer drug carriers is the almost exclusive uptake of liposomes by cells of the liver and spleen, thus allowing only an insignificant portion of the therapeutic dose to reach the diseased target area. Thus, any strategy for homing can only be successful if premature clearance of the injected dose by these tissues can be prevented or delayed. Such a delay appears possible by the simultaneous administration of a large quantity of empty liposomes or by the use of positively charged liposomes exhibiting a slower rate of elimination from plasma. It is also established that homing of liposomes by the use of target cells is possible. When IgG immunoglobulins raised against a variety of normal and malignant cells were co-entrapped (in their radiolabeled form) with In-labeled bleomycin in liposomes, the uptake of bleomycin, IgG, and the liposomal carrier was most pronounced when liposomes were associated with the IgG corresponding to the cell type studied. Thus, the potential for targeting anticancer drugs to specific sites of action via liposome carriers may be realized by the development of techniques for blocking hepatic uptake of liposomes and immunological techniques for homing the drug to its site of action. (19 refs)

357. THE DRUG-CARRIER POTENTIAL OF LIPOSOMES IN CANCER CHEMOTHERAPY (MEETING ABSTRACT).

Gregoriadis G
Clincial Research Centre, Harrow, Middx. HA1 3UJ. U.K.
Abstracts Of Papers, 9th Int Congr Chemother. Letchworth, Hertfordshire, The Garden City Press, Inc., 1975.

Successful treatment of cancer is often hampered by the failure of the administered agents to reach diseased areas of the body without at the same time affecting normal cells. A drug-carrier which would upon injection direct drugs to target cells should be of considerable value. It has been suggested that phospholipid vesicles (liposomes) could be employed as carriers of enzymes or drugs in the treatment of disease. Indeed it appears that control of the fate of agents administered via liposomes is feasible. Following injection into the blood, liposomes localize in the lysosomes of the liver and spleen where they are disrupted. Liposome-entrapped agents are thus liberated and act either locally or, after escape from lysosomes, in other cell compartments (eg nucleus). Experience with cancer patients has shown uptake of liposomes by tumor cells as well and a strategy has been developed recently by which liposome-entrapped agents can be homed to target tumor cells by liposome-associated antibodies which exhibit a specific affinity for the surface of these cells. (Author Abstract)

358. POTENTIAL OF LIPOSOMES IN CANCER CHEMOTHERAPY (MEETING ABSTRACT).

Rahman YE
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439

Cancer Immunol Immunother; 3(Suppl):S23 1977

Many studies have indicated the usefulness of liposomes for delivery of drugs, particulary antitumor agents. We have compared the toxic effects in mice of nonencapsulated and liposome-encapsulated antitumor drugs. Significant protection by liposome encapsulation has been observed in the following cell systems: (1) WBC, (2) nucleated cells of the bone marrow, (3) colony-forming stem cells of the spleen and bone marrow, (4) the proliferating intestinal cells, and (5) the antibody producing cells of the spleen. The lower toxicity of nonencapsulated than liposome-encapsulated drugs, however, cannot be explained on the basis of drug uptake in bone marrow, spleen, and intestine. Possible applications of liposome-encapsulated antitumor drugs for therapy of tumors that have become drug resistant, due to altered membrane permeability, will be presented. Potential use of liposomes to transport antitumor drugs that are not water soluble will also be discussed.

359. POTENTIAL APPLICATIONS OF LIPOSOMES TO THERAPY (MEETING ABSTRACT).

Ryman BE
Charing Cross Hosp. Medical Sch., Univ. London, London, England

Conference on Liposomes and Their Uses in Biology and Medicine Seminar held in New York, N Y, September 14-16, 1977 The New York Academy of Sciences, New York, NY, 1977.

The possibilities of liposomes as therapeutic vehicles have moved from their original field of enzyme carriage to other areas including their role as adjuvants, in vaccine preparation, in drug delivery and in hormone administration. Work from this laboratory in the following areas will be presented. (a) The treatment of a child with lysosomal glycogen storage disease (Pompe's) with iv administered liposomally-entrapped amyloglucosidase. (b) The uptake of iv administered 99mTc-labelled liposomes in tumor-bearing animals and patients - leading us to conclude that, whereas certain animal tumors accumulate liposomes, particularly small anionic ones, similar observations have not been made in the patients. (c) The uptake by regional lymph nodes following interstitial injection in rats - suggesting that liposomes may be useful for diagnosis and therapy. (d) Following the first experimental data from this laboratory on the effects of liposome-associated insulin by the oral route, there is now evidence suggesting that liposomes may protect insulin from degradation by gut proteolysis. (e) Negligible absorption after oral administration of inulin, antibiotics, polyethylene glycol or certain anti-inflammatory esters has been observed. (no Refs)

360. CANCER CHEMOTHERAPY BY CONSIDERING THE SPECIFICITY OF CANCER CELLS AND TISSUES: IMPROVEMENT OF THE EFFECTS OF CANCER CHEMOTHERAPY USING LIPOSOMES.

Yamanaka N, Koizumi K, Ota K
Lab. Chemotherapy, Aichi Cancer Center, Chikusa-ku, Nagoya 464, Japan

Gan To Kagaku Ryoho; 6(2):225-230 1979

The probability of specific chemotherapy for cancer cells and/or tissues is discussed in relation to the versatility of liposomes as carriers of drugs. The usefulness of liposomes as carriers of pharmacologically active agents for cancer chemotherapy is as follows: protect anticancer drugs from inactivation; change the pharmacokinetics of liposome-encapsulated antitumor drugs and tissue distributions; introduce as carriers anticancer drugs into resistant tumor cells; differentiate liposome distribution in tissue by modification of liposome components (lipids, glycoproteins, lectins, etc). (Author abstract) (47 Refs)

361. APPROACHES TO EFFECTIVE ANTI-CANCER DRUGS.

Neidle S
Dept. Biophysics, King's Coll., London, England

Nature (Lond); 268(5617):195-196 1977

This brief review of the effective use of anticancer drugs discusses the DNA-daunomycin (DN) complex, *liposomes* as drug carriers, the DN-DNA model, and new DN derivatives. (no Refs)

362. POTENTIAL FUTURE APPLICATION WITH THERAPEUTIC AGENTS.

Atkins HL
Dept. Radiology, Health Sciences Center, State Univ. New York, Stony Brook, NY, 11794

Semin Nucl Med; 9(2):121-130 1979

Several new approaches to radiation therapy with radionuclides have been discussed. Fe55 is selectively utilized in the RBC developmental cycle and, in therapeutic doses, can lower marrow and circulating RBC levels with much smaller degrees of effect on other cell lines. A serious complication, noted in animal studies, is the induction of neoplasms, especially osteosarcoma. Selective irradiation of the cell nucleus is possible with 125I-iododeoxyuridine. This results in highly efficient cell killing due to the highly concentrated region of ionization. High concentrations of densely ionizing radiation in the malignant cell may also be accomplished with 211At. The use of *labeled liposomes* is an additional approach to the delivery of intracellular irradiation. None of these approaches is applicable for the practical treatment of human malignancy at the present time. The importance of these approaches is their value as models for future development of methods that can provide highly selective radiation to target sites. (Author abstract) (52 Refs)

363. INCREASED SELECTIVITY OF DRUGS BY LINKING TO CARRIERS.

Trouet A
Laboratoire de Chimie Physiologique, Universite de Louvain, avenue Hippocrate, 75, B-1200 Bruxelles, Belgium

Eur J Cancer; 14(2):105-111 1978

The usefulness of carriers for many types of drugs is discussed. Drug-carriers result in a higher selectivity of action, but non-permanent carriers are not usable in oral or topical administration. The carrier should be non-toxic, non-immunogenic, and biodegradable. For an extracellular site of action, carriers should have a size that prevents crossing of endothelia and capillaries, not be captured too much by macrophages and the reticuloendothelial system, and be small enough to be excreted by the kidneys. Intracellular action can be achieved by selective extracellular release in certain pathological conditions, and by intracellular release. Lysomotropic drug-carriers penetrate the cell by endocytosis. *Unilamellar lipid vesicles* can penetrate cells by fusing with cellular membranes. Possible selective carriers are antibodies, peptidic hormones, viral envelopes or surface components, lectins, selectively endocytized macromolecules, and polypeptidic fragments of toxin. Examples of drug-carrier complexes with increased selectivity are given. (40 Refs)

364. TARGETING OF DRUGS.

Gregoriadis G
Div. Clinical Investigation, Clinical Res. Centre, Watford Rd., Harrow, Middlesex HA1 3UJ, England
Nature (Lond); 265(5593):407-411 1977

The development of carriers for anticancer drugs is discussed, with special attention to *liposomes*. Antitumor drugs complexed to antibodies have increased cytotoxicity to malignant cells possessing antigens corresponding to the immunoglobulin carrier. The difficulties associated with this method are the isolation of target-specific antigens and the purification of immunoglobulin molecules specific for the antigen. The antigen-recognition site of the protein may also be masked by the drug, or the patient may be allergic to the carrier. Some sialoglycoproteins exhibit an affinity for hepatic parenchymal cells and others may be useful as carriers of drugs to the kidney. Other possible carriers are trophic hormones, lectins, and some lysosomal enzymes. DNA, RBC, and WBC have also been used as carriers. Insoluble polar phospholipids form ordered assemblages of lipid bilayers (liposomes) in the presence of water, and these layers can be used to carry drugs to target areas. Further development of this method requires that ways be found to reduce hepatic and splenic interference with this mechanism and to manipulate the size and composition of the liposomes so as to allow them to pass a variety of anatomical barriers. Liposomes deliver drugs to the lysosomes in vivo and in vitro and can fuse with cell membranes in vitro. These characteristics make liposomes possible carriers for anticancer drugs. (110 refs)

365. USE OF LIPOSOMES FOR DIRECTED TRANSPORT OF DRUGS TO ORGANS AND TISSUES.

Ladygina GA, Tentsova AI, Zizina OS
All-Union Res. Inst. Pharmaceutics, Moscow, USSR
Farmatsiia (Mosk); 27(6):52-57 1978

This review summarizes literature pertaining to the use of liposomes for the directed transport of various drugs to target organs. Incorporation into liposomes changes the pharmacokinetics of some drugs and thus enhances their efficacy. For example, the incorporation of bis-chloroethylnitrosourea into liposomes potentiates its effect in the treatment of Ehrlich ascites carcinoma and L1210 leukemia in mice. (43 Refs)

366. DRUG LATENTIATION IN CANCER CHEMOTHERAPY.

Workman P, Double JA
MRC Clinical Oncology and Radiotherapeutics Unit, Medical Sch., Hills Road, Cambridge CB2 2QH, England
Biomedicine; 28(5):255-262 1978

One attempt to improve the selectivity of antitumor agents involves the use of agents with latent activity. These prodrugs are relatively inactive until converted to their active forms in vivo, either spontaneously or by the action of enzymes, in normal host tissues or tumor tissues. Many agents thus far tested for selective activation by tumor tissues are ineffective because of the unfavorable distribution of activating enzymes among normal and tumor tissues. In designing new agents, the activities and properties of these enzymes in normal and tumor tissues, in both animals and man, must be compared. Enzyme activity measurements should not be made from tissue homogenates. Since clonogenic and non-clonogenic tumor cells seem to have different enzyme levels, it may be feasible to develop latent cytotoxic agents that are activated by clonogenic tumor cells, but not by intestinal or marrow stem cells. The use of 'lysosomotropic' agents has been recommended to exploit the reportedly high endocytotoxic activity and high lysosomal enzyme activities of many tumor cells. According to this hypothesis, a cytotoxic agent attached to a high mol wt carrier is selectively endocytosed by tumor cells and hydrolyzed by their lysosomal enzymes, leading to the delivery of a high concentration of the agent to the tumor cells. Possible carriers for latent agents include DNA, *liposomes*, and RBC. Greater selectivity may be obtained by complexing cytotoxic agents with tumor-specific antibodies or peptide hormones. The mechanism of action of these agents is unknown, but it may involve a combination of antitumor targeting and selective release of the agent by tumor enzymes. (118 Refs)

367. CONCEPT OF PHARMACOSOMES: A NEW APPROACH TO THE DEVELOPMENT OF DRUGS.

Raikhman LM, Moshkovskii IuSh, Piruzian LA
Res. Inst. Biological Testing Chemical Compounds, Moscow Oblast', USSR
Khim Farm Zh; 12(4):18-22 1978

Possibilities in the development and use of highly selective bodies (by analogy with liposomes, called pharmacosomes) that can introduce specific biologically active agents into the target cell are discussed. The pharmacosomes should consist of effectors, detectors, and factors that allow for permeation of the pharmacosome into the target cell. (27 Refs)

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